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BONE DISEASES

in Medical Practice

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Preface

IN RECENT YEARS EXTENSIVE INVESTIGATION in the field of skeletal diseases has clearly shown that bone, like other tissues, enters into the vital metabolic processes of the body The skeleton no longer can be considered to act solely as a static, supporting framework of the body The latter function, of course, is of paramount importance for health and well-being but we must not overlook that bone lives, is constantly changing and markedly influences many of the vital functions of the organism.

The viable portion of bone is made up of a characteristic cellular population living in an intricate and specific protein-carbohydrate environment referred to as the bone matrix. In this matrix the inorganic bone salts are deposited. The metabolic importance of the large amounts of calcium and phosphate that are liberated during pathologic resorption of bone has been known for several decades. We now recognize that in both the healthy and the diseased skeleton the protein bone matrix, too, is the site of many metabolic processes that are just as important as the well-known changes of calcium and phosphorus metabolism. In this way the metabolic role of the skeleton may be considered to be as significant as its supportive function.

Recently the availability of radioisotopes has afforded rich opportunities to explore the normal and pathologic physiology of bone and bone marrow previously inaccessible to investigation. Moreover improved laboratory techniques have markedly refined the clinical differential diagnosis of bone diseases and new therapeutic measures have been introduced. This may, at least partly, be responsible for the recent wave of enthusiasm of the general medical profession for this chapter of medicine. It was only a few years ago that the following sardonic observation seemed justified

> When budding physicians are first introduced to osteology the skeleton seems to be only a collection of oddly shaped tubes and plates consisting of calcium carbonate and calcium phosphate Most members of the medical profession cherish this first impression for the rest of their lives.

Fortunately this attitude has radically changed and the general physician is no longer of the opinion that the knowledge of skeletal diseases represents an esoteric chapter of medicine, falling within the province of the orthopedist, the radiologist, or the "medical bone specialist."

The author has become vividly aware of the mounting interest shared by all members of the medical profession for this phase of medicine. He has had numerous opportunities to share this interest with varied audiences, and it is because of such general enthusiasm for this subject that the present book was written. In its actual format this volume has one major objective to present the subject in such a way that it can be used in the daily practice of medicine, emphasizing that in many skeletal diseases a clear-cut diagnosis can be made which will usually point the way to rational and often remarkably rewarding therapy

As is always the case in the preparation of a book on bone diseases, the writing of the manuscript is difficult, the reproduction of the representative roentgenograms a heartbreaking task. The x rays illustrating the text have been culled from collections of many different hospitals located in three different continents. I am deeply obliged to many of my colleagues who have helped me find the roentgenologic material that would satisfy the technical requirements necessary to obtain good, sometimes even excellent, reproductions. The technical part of the new photo-electronic methods employed for the improvement and the reproduction of roentgenograms was in the able hands of Mr

Robert Carlin. The publisher has gone to great lengths to find an adequate method, in this case the gravure process, for the reproduction of the roentgen photos in book form. Only the reader can decide whether such additional effort has been rewarded.

This book, therefore, is the end result of the efforts and the interest of many medical and non-medical colleagues and friends. The author can only assure all of them that he will never forget their valuable help and their continuous encouragement.

Chapter 1

Physiology of Bones

For many years it was generally believed that the skeleton, in the depths of which living bone marrow is hidden, served solely as a support for surrounding organs. Today, however, it is clearly recognized that only 70 per cent of the bone substance consists of inorganic salts. The other 30 per cent—some authors label it 50 per cent—is made up of living tissue that has a complicated metabolism. This is the so-called bone matrix, consisting of an amorphous ground substance and highly differentiated fibers. In the bone matrix both specific proteins and carbohydrates are present. Bone is formed by deposition of bone salts in this matrix.

Apart from bone matrix and bone salts, the bone substance contains living cells—osteoblasts, osteocytes and osteoclasts.* The osteoblasts are found on the surface of the bone trabecules, the osteocytes are osteoblasts surrounded by calcified bone matrix, and the osteoclasts are multinuclear giant cells which nowadays are considered to be formed by the fusion of osteoblasts. Osteoblasts form bone matrix, osteocytes serve to maintain the bone and osteoclasts participate in the dissolution or resorption of bone. Osteoclasts live only a short time, probably 36 hours the life span of osteoblasts is much longer One osteoclast destroys in 36 hours the amount of bone which ten osteoblasts can produce in 10 days. It follows that if, in histologic bone sections, one osteoclast is present for every few osteoblasts, excessive bone destruction must be going on. Osteoblasts form an alkaline phosphatase, while osteoclasts allegedly produce an acid phosphatase.

BONE MATRIX

Part of the collagen—the specific protein moiety of the bone matrix—is present in amorphous form. The rest of the collagen is arranged in fibers which, when studied with the electron microscope, prove to consist of bundles of fibrils. These collagen fibrils, with a diameter varying between 200 and 2000 A (angstrom units*), have a characteristic band structure. The distance between the principal bands is always the same—640 A.

Collagen contains considerable amounts of glycine, glutamic acid, proline, hydroxyproline and small quantities of other amino acids. Hydroxyproline and hydroxylysine are the characteristic components of collagen, because these two amino acids are found only in collagen and not in blood serum. No cystine, cysteine or tryptophane are present in collagen. Collagenases, enzymes which can break down unaltered collagen, are rarely encountered in nature and have not been demonstrated in the skeleton. The only known sources of collagenases are B subtilis and two different strains of clostridium. Fresh unaltered collagen is resistant to proteolytic enzymes, but the latter can digest collagen which has first been denatured by acid, alkali or heat.

The carbohydrates of the bone matrix belong to the group of the mucopolysaccharides. The prevailing ones are chondroitin, chondroitin sulfate and hyaluronic acid, but the presence of other mucopolysaccharides has been proven In the ground substance of the bone matrix, compounds of collagen and mucopolysaccharides are present which are

*One angstrom unit is one ten millionth of a millimeter

able to initiate calcification, both in bone matrix and in cartilage.[14,21]

Whereas the primitive collagen fibril itself does not contain any mucopolysaccharides, the latter substances are found in the collagen fibers, which consist of hundreds of fibrils.[17] These fibrils are kept together by a cement substance, and the mucopolysaccharides are probably present in the latter material.

In histologic preparations, the bone matrix presents in the form of osteoid. Due to the presence of mucopolysaccharides, osteoid in fixed preparations stains metachromatic with toluidine blue, the osteoid appears reddish, whereas the rest of the tissue stains blue. The metachromasia disappears under the influence of hyaluronidase.

BONE SALTS

The main part of the bone salts consists of calcium and phosphate, in a relation of 1 2. About 99 per cent of the total body stores of calcium, 90 per cent of the citric acid, 30 to 40 per cent of the sodium, 25 per cent of the body water and considerable amounts of magnesium, fluoride and other essential electrolytes are found within the skeleton and the teeth.

The precise chemical constitution of the calcium phosphate compound of bone is still debatable. Formerly it was surmised that bones consists of tertiary calcium phosphate to which magnesium phosphate, calcium carbonate and calcium fluoride had been adsorbed. Later it was believed that the bone salts closely resemble the mineral apatite, a hexagonal calcium phosphate. Recent evidence indicates that the molecules of the bone salts contain a considerable number of hydroxyl groups. For the time being it is accepted that the bone salts consist of a hydroxyapatite, that is, a hexagonal tricalcium phosphate with hydroxyl groups fixed on the corners of the molecule. In addition, fluoride, phosphate, carbonate, bicarbonate, citrate, sodium, magnesium and potassium are adsorbed to the hydroxyapatite molecule. Other mineralogists, however have vigorously defended other structural formulas for the bone salts—hydrated tricalcium phosphate, for example.

In bone, the hexagonal hydroxyapatite microcrystals, measuring 200-300 by 20-50 Å, are arranged in long columns within the ground substance and form rings around the collagen fibers.[19] Ultimately, a lattice structure results in which one gram of bone salt is spread over a tremendous surface, which is said to vary between 106 to 200 square meters. Inasmuch as the calcium content of the skeleton of the adult varies around 1500 grams, the whole surface area of an adult male skeleton must amount to more than 100 acres. This vast surface is bathed by a few liters of body fluids. It was generally believed that the entire outer surface of the crystals—about 14 per cent of the total crystalline mass—could partake in surface chemical exchanges. Thus, the opportunity for a rapid transport of different ions from the extracellular fluid to the surface layers of the tremendously expanded bone substance seemed practically unlimited. Recent measurements, however, indicate that in a normal adult man the total amount of skeletal calcium available for exchange does not exceed five to six grams. Since this quantity amounts to less than one half of one per cent of the total calcium of the skeleton, it is apparent that only a fraction of the theoretical crystal surface can participate in the rapid exchange of calcium from the extracellular compartment to the surface of the skeleton.[8]

PHYSICAL CHARACTERISTICS OF BONE

The collagen fibers of the bone matrix are organized in the form of regular lamellae, which fit snugly between the columns of calcium salts. This arrangement is similar to the structure of reinforced concrete, plywood and laminated plastics. The remarkable re

sistance of bone to both compression and tension is due mainly to this spatial relationship between the bone matrix and the plates of hydroxyapatite. Not only is bone three times stronger than wood, but the tensile strength of bone is nearly as great as that of cast iron. In addition, lumbar vertebrae can withstand a pressure of *600-900 lbs. per square inch.* This rare combination of marked resistance against both tensile and compression forces is hardly ever found in building materials.[8]

In this connection, the remarkable mechanical characteristics of the intervertebral disks may be mentioned. Increasing loads up to 100 kilograms cause only negligible changes in the configuration of the lumbar disks.[11] Under such a load, the compression of the disk does not exceed 1.4 millimeter, the expansion, 0.75 millimeter. There is a fundamental difference, however, between the results of a continuous compression and a sudden trauma of short duration to the vertebra. After a sudden blow, an intervertebral disk starts to oscillate. These remarkable oscillations occur even if a sudden short blow is directed against a disk which previously *had been placed under a static load of 130* kilograms. In this way, the intervertebral disks represent a shock absorbing apparatus that protects the structure of the vertebral column. In the higher age groups the ratio *between the amounts of collagen* and poly saccharides present in the disks changes. This leads to decreased water content, which impairs the shock-absorbing capacity of the intervertebral disks.[13] Thus, in older individuals the vertebral *column* becomes *more* and *more* vulnerable to trauma.

USE OF RADIOISOTOPES FOR THE INVESTIGATION OF BONE PHYSIOLOGY

The introduction of isotopes into experimental medicine has provided extremely valuable tools for the investigation of the physiology of the skeleton. Both radioactive calcium (Ca^{45}) and radioactive phosphorus (P^{32}) have introduced new approaches to the investigation of the deposition and absorption of the inorganic bone salts. Investigation of other "bone-seeking" isotopes has led to the conclusion that both Sr^{85} and Ba^{140} can be used for the same purpose. Since chondroitin sulfuric acid contains sulfur, radioactive sulfur (S^{35}) has been employed to obtain a better understanding of some of the problems connected with the mucopolysaccharide component of bone matrix. Radioactive carbon (C^{14}) has been used in animal experiments to analyze *the collagen* part of the bone matrix.

The first experiments with oral administration of radioactive calcium to rats showed that within 45 hours 50 per cent of the total skeletal calcium was exchanged for calcium of the body fluids.[14] These exchanges of calcium were much less marked in rats 15 to 20 weeks of age than in rats 3 to 6 weeks old. The phosphate and the sodium of the bone also are subject to comparable rapid changes. Carlsson, Bauer and associates found that the greater part of the tracer substances which can be discovered within the skeleton after injection are only adsorbed on the surface of the bone crystals.[2] At best, the tracer substances are dissolved in the watery phase, which is always present within the crystals. These exchange reactions are reversible; thus, a large part of the rapidly absorbed tracer substances leaves the skeleton nearly as quickly as it had been adsorbed. This rapid exchange of tracer substances between bone and surrounding tissue fluid must be distinguished from true crystallization of the injected Ca^{45} in the form of hydroxyapatite. The latter process—the participation *of injected radiocalcium* in the formation of bone salt—has been designated "accretion."[10]

In the same way, the rapid liberation of the loosely adsorbed injected mineral must be distinguished from actual bone resorption or dissolution *of bone salt. It was* found that in the tibia of young rats, 2.0 milligrams of calcium per hour were adsorbed in exchangeable form. In contrast to this large quantity, the actual accretion of calcium—that is, the

deposition of calcium in nonexchangeable form—amounted to only 0.17 milligram per hour. The net increase of the total calcium content of the tibia was 0.04 milligram per hour. It follows that in the tibia of the young rat, when 0.17 milligram of calcium per hour was deposited, 0.13 milligram of calcium was resorbed.

In this way it could be ascertained that ingested calcium and phosphate do participate in the growth of the crystal lattice of the bone minerals, and that continuous resorption and crystallization of part of the bone salts take place. Experiments with growing animals have led to the conclusion that after 50 days, 29 per cent of the bone salt of the femoral and tibial epiphyses were renewed. In the diaphyses this value amounted to only 7 per cent. Measurements of accretion and resorption rates of Ca^{45} thus enable us to make a study of metabolic processes that would not be possible by the use of measurements of net increase of calcium content alone.

The weak beta radiation and long half life (about 150 days) of the commonly available calcium isotope Ca^{45} makes it impractical to use this isotope in humans. Not only is it hard to measure the weak radiation following low dosage, but, in addition, Ca^{45} may be dangerous because of possible long term irradiation damage following high dosage. In the near future, another calcium isotope (Ca^{47}) may become available, and, since this isotope has a six-day half life and is a pure gamma-emitter, it may permit isotope studies of skeletal calcium metabolism in humans on a routine basis.

P^{32} has been used for studies of bone salt metabolism in normal and rachitic children. For such a purpose, the accretion rate in the upper part of the tibia of children who had received P^{32} was determined from bone biopsies of this region. It was found that the accretion rate of phosphorus of the bone sample decreased with age. Moreover, in vitamin D–deficient children, the accretion rate was lower than in normal children of the same age. Following the administration of vitamin D to the rachitic children, the accretion rate rose to about normal values.

Considerable caution must be exercised before the results of experiments on rats can be used to explain physiologic and pathophysiologic observations in humans. The structure of the bones of adult rats is different from the skeleton of other animals, because in the epiphyses of the adult rat—and even the old rat—cartilage always persists. Thus, the turnover of the minerals in the epiphyseal part of the bones of the adult rat is more intense than that of other animals. This applies also to man, in whom the epiphyses no longer contain cartilage. The experiments of the Swedish scientists show that the accretion of bone salt in the proximal part of the tibia of normal infants is five times slower than it is in the epiphyses of the tibia of young rats.

Both the accretion rate of calcium and the deposition of exchangeable bone salt are higher in young individuals than in old persons. The same differences are encountered in a fractured bone, as compared to an intact control bone. It seems possible that some of the exchangeable calcium, located on "crystal surfaces," becomes unavailable for exchange later in crystal life.

By the use of modern techniques, roentgenograms can be made of the microscopic structure of bone disks that have been carefully ground to a thickness of 50 micra. Such microroentgenograms permit precise study of differences in the calcium content of the osteons.* This method reveals that about 10 per cent of the osteons of adult dogs are incompletely calcified. These presumably are the young osteons. When the animal has previously been injected with Ca^{45} the radioactivity of the osteons of the bone disks can

*An osteon or a haversian system consists of a narrow haversian canal containing blood vessels surrounded by a thick wall of concentric bone lamellae.

be determined with the help of radioautographic images. Combined studies of microroentgenograms and radioautographs of the same areas demonstrate that radioactivity appears only in the radioautographic images of the young, partly calcified osteons, but not in the completely ossified older osteons of compact bone.[4,18] These incompletely calcified osteons represent the metabolic part of the skeleton where calcium and phosphorus derived from the intercellular fluids are deposited. The other 90 per cent of the osteons are completely calcified and actually serve as the solid mainstay of the body. This part of the skeleton influences calcium and phosphorus metabolism only when abnormal local erosion of bone occurs.

Ingestion of radioactive phosphorus (and of radiocalcium in selected cases) reveals that in the skeleton of a normal adult man the accretion-resorption rate of the calcium averages about 0.5 gram per day. If the skeleton contains about 1500 grams of calcium and accretion-resorption took place at a uniform rate in all parts of the skeleton, it would take about 3000 days to replace all skeletal tissue. Most of this accretion resorption process of calcium must occur in the young and active osteons of the adult skeleton. Since these osteons comprise about 10 per cent of the total amount of osteons of adult bone, the calcium of the active osteons may be renewed in about 300 days. These active osteons are especially concentrated in the metaphyses,* which is the reason the metabolic turnover is considerably faster in the epiphyses than in the shafts of the long bones, even after closure of the epiphyseal line. It is therefore probable that in adult humans, rebuilding of the entire diaphysis of the femur as a result of the normal accretion-resorption processes must take 25 years or more. In contrast, more than 50 per cent of the sodium stored in the skeleton is renewed within a period of 10 days.

*The metaphysis is the part of the diaphysis adjacent to the epiphysis.

Studies of this type give some quantitative background to radiographic observations on the rate at which the skeleton loses and gains in density during development and eventual reversal of osteoporosis (p. 21). They also show why the bone seeking fission products are more dangerous than those which are taken up by the soft tissues. Once Sr^{90} (half life about 25 years) is incorporated in the skeleton, it stays there virtually for life.

After injection of radioactive sulfur (S^{35}) in adult dogs, only the incompletely calcified osteons become radioactive.[16,71] This indicates that not only calcium deposition but also the greater part of the new formation of mucopolysaccharides takes place in young osteons. The latter conclusion can be confirmed by direct metachromatic staining of the bone disks. Again, the incompletely calcified young osteons contain by far the largest part of the metachromatic staining substance, presumably chondroitin sulfuric acid.

Introduction of radioactive carbon in growing rats is followed by the appearance of radioactive granules below the periosteum of the diaphyses and the endosteum of the metaphyses. The radioactive granules, found after introduction of radiocarbon, do not disappear under influence of either the diastatic enzymes from saliva or hyaluronidase. This excludes the possibility that the C^{14} has been deposited either in glycogen or in mucopolysaccharides. It is therefore accepted that the C^{14} is introduced into the growing collagen fibers.

In view of the results of these experiments, it is now believed that the rapidly growing part of the bone matrix (and therefore of the bone) is spread over a funnel shaped area. The wide part of the funnel is situated in the subperiosteal part of the diaphysis, the stem of the funnel is located in the subendosteal part of the metaphysis. This funnel-shaped area of young osteons is surrounded by old osteons in which under normal circumstances metabolic changes no longer take place.

BONE FORMATION

For many decades, bone formation was believed to depend upon the supersaturation of the calcium and phosporus content of the intercellular fluid, which would favor the precipitation of calcium phosphate. As a matter of fact, serum as such is an undersaturated solution of secondary calcium phosphate, but this undersaturation exists only in the absence of a solid phase. If serum is in contact with a solid phase, i.e., with hydroxyapatite crystals, it is supersaturated.[10a] This fact helps to explain the growth of bone.

As far as endosteal, periosteal, and membranous bone formation are concerned, the protein component of the bone matrix plays an important role in bone formation. It has been shown over and over again that when collagen preparations are brought in contact with serum, hydroxyapatite precipitates. Since the deposition of hydroxyapatite takes place exclusively in the matrix, it follows that bone formation is possible only when a sufficient amount of bone matrix is present. Thus, when no organic osseous matrix is manufactured, the daily wear and tear gradually leads to atrophy of the bone.

The bone matrix is also responsible for the physical orientation of the inorganic crystalline components of the bone. Feitelberg[7] using x ray diffraction, demonstrated that the longitudinal direction of the collagen fibers of a partially decalcified femur runs parallel with the crystallographic c-axis of the hydroxyapatite crystals. He then completely decalcified a femur sealed one end with paraffin, filled the lumen of the decalcified tubular bone with calcium chloride solution and sealed the other end of the bone with paraffin. Thereafter the whole preparation was immersed in a sodium phosphate solution for thirty days. Calcium diffused slowly into the bone matrix from within, phosphate diffused from without, and calcium phosphate precipitated in the decalcified bone. After thirty days the femur was washed in water X ray diffraction at that time revealed that the calcium had precipitated in the form of hydroxyapatite, just as it precipitates in living bone. In addition, the c-axis of the hydroxyapatite crystals again ran parallel to the axis of the fibers of the bone matrix. Both the form of crystallization and the physico-chemical structure of the calcium salts of the bone followed a special pattern which directly depends upon the specific qualities of the bone matrix.

Even if there can be no doubt that for the formation of bone the collagen of the bone matrix is of paramount importance, it must be recognized that chondroitin sulfuric acid of the bone matrix also plays an important role. All tissues—not only cartilage and bone matrix, but also arteriosclerotic plaques, renal stones and calcified scar tissue—in which calcium is deposited contain this mucopolysaccharide.[14] It has been recently suggested that chondroitin sulfuric acid may well act as a cation exchange resin, capable of concentrating calcium and other cations. The incredibly large surface area of the skeleton certainly facilitates such cation exchange.

Even if our actual knowledge of endosteal, periosteal, and membranous bone formation is only superficial, our lack of understanding of the mechanism of enchondral ossification is still more discouraging

Enchondral bone is formed in the metaphyseal part of the epiphyseal disks, where no matrix is present and where the pre-existing hyaline cartilage contains hardly any glycogen, phosphatase or enzymes that are able to split long carbohydrate chains—all substances which are generally regarded as indispensable for enchondral bone formation.

The appearance of glycogen in cartilage in the course of the initial stages of ossification may well be of importance, since the presence of glycogen and phosphate permits the formation of organic phosphates.[3] These data would seem to lift a tiny corner of the veil that hides the secrets of enchondral ossification, were it not that glycogen and enzymes appear only *after* ossification has actually started.

It is quite possible that Sobel's complex of collagen and chondroitin sulfate[11] may be a major factor in the dynamics of enchondral ossification. Different complicated histologic processes ultimately lead to the formation of columns of osteoid, manufactured by the osteoblasts. In these columns of osteoid hydroxyapatite crystals are deposited, bringing about the formation of parallel, vertical rows of primary bone trabeculea. As soon as the infant starts to move around, these primary bone trabecules are reabsorbed and replaced by the secondary spongiosa. The new bone trabecules are arranged in the form of girders of a vault, which serve to transfer to the shaft the strains and stresses to which the skeleton is continuously subjected. Modifications of the arrangement of the pattern of the bone trabecules continue during life. Since such changes necessitate destruction and reconstruction of a certain number of trabecules, moderate quantities of bone substance must be released every day by osteoclastic resorption and replaced by osteoblastic action. This is the so-called daily wear and tear of the skeleton. This incessant resorption and deposition of bone which, at first sight, might appear aimless and even redundant, is nevertheless of the utmost importance. It safeguards the resilience of the skeleton by modifying the spatial orientation of the trabecules until the highest degree of effective solidity is obtained.

Osteoblastic activity starts in utero, but osteoclastic resorption does not occur before the infant is eight months old. At this time, the attempts to walk require the resorption of the primary bone trabecules by osteoclasts to be replaced by the mechanically better adapted secondary trabecules. Thus, a certain degree of osteopetrosis exists temporarily in young infants, because the osteoblastic bone deposition is not held in check by osteoclastic activity

A connection between alkaline phosphatase and bone formation must exist, because phosphatases are always present when normal or pathologic bone formation takes place However, the concept that inorganic phosphate, formed from organic phosphoric esters by the action of phosphatase, plays an important role in the ossification of cartilage, is all but proven. As a matter of fact, cartilage contains so little hexose phosphate that after hydrolysis by phosphatase, only traces of inorganic phosphate would become available.

A new approach to the problem has been developed since Engfeldt and Zetterström[8] in 1954 described a congenital skeletal disease in which retarded growth clinically resembled severe rickets. Renal damage was also present, together with hypercalcemia and a significant decrease of the alkaline phosphatase of the serum to 20-40 per cent of the normal values. The mineralization of the newly formed bone matrix was greatly defective. It is obvious that there must be a connection between the hypophosphatasemia and the defective calcification of matrix.

For years, the discussion had centered upon the question whether the action of alkaline phosphatase upon hexose phosphate esters could liberate the phosphate, this action being necessary for the initiation of the ossification of the matrix. McCance, Morrison and Dent[18] now mention the possibility that alkaline phosphatase might liberate phosphate by the hydrolysis of phospho-ethanolamine and not of hexose phosphate esters. In patients with hypophosphatasemia, the urine contained considerable amounts of phospho-ethanolamine, whereas this substance was not excreted by normal persons. One could thus speculate that under normal circumstances the alkaline phosphatase hydrolyzes phospho-ethanolamine and that the liberated inorganic phosphate is used for calcification of cartilage. In hypophosphatasemia the alkaline phosphatase of the body is markedly decreased, and no phosphate is split off from phospo-ethanolamine. In the absence of phosphate, the calcification of the matrix would be impaired, and the unchanged phospho-ethanolamine would appear in the urine.

METABOLISM OF CALCIUM AND PHOSPHORUS

A normal interplay exists between intestinal absorption, calcium excretion, resorption of calcium from and deposition of calcium in the skeleton. If the demands of the skeleton for deposition of calcium in new bone matrix are diminished, an increased amount of calcium may be excreted. Increased excretion of calcium must come either from the stores of calcium of the skeleton or from accelerated intestinal absorption of calcium. Thus, a direct interrelationship exists between the needs of the skeleton and the calcium balance. Calcium is normally excreted both by the gastro-intestinal tract and by the kidneys. In normal persons, about 30 per cent of the calcium excreted is in the urine, 70 per cent is in the stool. Calcium is also lost from the maternal organism during the formation of the fetal skeleton and lactation. The normal value of calcium in serum varies between 9 and 11 mg. per 100 cc., the inorganic phosphorus of the serum between 3 and 4 mg. per 100 cc., and the alkaline phosphatase between 3 and 4.5 Bodansky units or 8 and 12 King-Armstrong units per 100 cc. In the absence of avitaminosis D the "threshold" for urinary excretion of calcium is about 7 to 8 mg. per 100 cc. of serum. In other words, when the serum calcium decreases below 7 mg. per cent, no calcium is excreted in the urine. Under these circumstances, all calcium is eliminated in the stool.

As a general rule, it can be stated that signs of tetany develop when the serum calcium drops below 6 mg. per cent. At the same time—at least, if the tetany is due to damage of the parathyroids—the serum phosphorus goes up to at least 6 or 7 mg. per cent. It may be added that hypocalcemia is much more important than the increase of inorganic phosphorus for the development of tetany. This follows from observations in cases of excessive losses of vitamin D and calcium in the stools, such as occur in fatty diarrhea. Here, also, signs of tetany appear when the serum calcium diminishes to less than 6 mg. per cent, although in this condition the organic phosphorus often decreases to levels below 3 mg. per cent.

The calcium of the blood is present only in the plasma; none is found in the erythrocytes. About half of the serum calcium is conjugated with protein, particularly with albumin, while the remaining serum calcium is ultrafiltrable, almost completely ionized in the form of calcium bicarbonate and calcium biphosphate. A negligible part of the ultrafiltrable serum calcium is not ionized, but is present as a complex citrate compound. Only the ionized calcium of the serum is physiologically active.

Until recently it was generally believed that the entire inorganic phosphorus content of the blood was ultrafiltrable and ionized. New experiments indicate, however, that this may hold true for only 75 to 80 per cent of the serum phosphorus. In addition, it is generally believed that when the serum calcium exceeds 15 mg. per cent, a complex colloidal calcium phosphate compound is formed which does not pass the glomerular membrane.

The relationship between the calcium ions, the carbon dioxide, the phosphates and the acidity of the blood serum has been expressed in the formula

$$\frac{Ca \times HCO_3 \times HPO_4}{pH} = K \text{ (constant)}$$

This so-called Howland-Kramer formula indicates that if the carbon dioxide and the pH of the serum remain constant, the product of the calcium and the phosphate content of the serum must always vary between 30 and 40.[1] But there are many conditions in which this formula is not valid. In avitaminosis D, *for example, both calcium and phosphorus* of the serum are usually low. When a patient with hyperparathyroidism develops uremia, the characteristic hypophosphatemia disappears and hyperphosphatemia results from the renal retention of phosphate. However under these circumstances the serum calcium

does not always decrease and, in certain cases of uremia due to hyperparathyroidism, hyper calcemia persists unabated. Hypercalcemia is also frequently encountered in generalized malignancies of the skeleton and in rapidly spreading multiple myeloma. In these patients the phosphorus of the serum is either normal or moderately increased, but certainly not depressed by the hypercalcemia. It is true that the combination of decreased serum calcium and high serum phosphorus occurs frequently in chronic uremia however, this combination of hypocalcemia and hyperphosphatemia depends upon other mechanisms, but not on the constancy of the product of serum calcium and serum phosphorus (p 89) The formula also does not explain the characteristic biochemical changes found in hyperparathyroidism. The decrease of the serum phosphorus in this disease is due to the excessive phosphorus excretion by the kidney the hyper calcemia to increased osteoclastic activity—both caused by increased production of parathyroid hormone.

There is no unanimous opinion regarding the amount of calcium which must be taken orally in order to keep a healthy individual in calcium balance. The vitamin D content of the body derived either from food or from exposure to sunshine, is of much greater importance for the calcium balance than is the calcium content of the food. As long as the vitamin D intake is satisfactory calcium equilibrium can be obtained even when the calcium ingested with the food is relatively small.

Whereas the National Research Council of the United States considers a daily intake of 800 to 1000 milligrams of calcium necessary for conservation of health, South African investigators are satisfied with a daily intake of 700 milligrams for men and 560 milligrams for women, French investigators, with 450 milligrams, and German nutritionists, with 400 milligrams. These differences depend mainly upon the daily calcium intake to which the peoples of the various countries are accustomed.

Since 99 per cent of the 1500 grams of c
cium stored in the adult body is present
the skeleton and teeth, the growth of
skeleton must be an important factor in
termining the calcium requirements of
body At birth the total calcium content
the body amounts to 0 8 per cent of the t
body weight. This percentage rapidly
creases until in the adult it has reached
per cent. Thus, the daily calcium requirem
for different age groups exhibits import
variations (see table 1) Children, for
stance, require relatively larger quantitie
calcium than adults.

TABLE 1

Age (in Years)	*Daily Calcium Requirement (in*
1	650
4	400
8	700
11	1100
14	1300
17	1000
18	700

During pregnancy the calcium requ
ment is far greater than under normal co
tions. The calcium intake of the pregnant
man must not only be sufficient for the nor
daily wear and tear of the maternal skel
but, in addition, it must provide the calc
necessary for building the fetal skeleton.
latter contains 23 grams of calcium at b
Moreover during the last trimester of p
nancy, significant amounts of calcium are
posited in the placenta. Finally, the calc
excretion in the urine of pregnant wome
often remarkably high. Thus, the daily
cium requirement for pregnant women r
at 1500 milligrams, at least for the sec
half of the pregnancy During lactation a
siderable amount of calcium is lost in
milk (400 milligrams per liter)[29] and the c
requirement for lactating mothers is th
fore increased to 2000 milligrams (p 35

When phosphates, fatty acids, and oxal
are present in the intestine in large amou
absorption of calcium is inhibited bec
of the formation of the relatively insol
calcium phosphates, calcium soaps and

cium oxalate, respectively The inhibition of calcium absorption by the presence of excessive amounts of phosphates in the intestine is one of the main causes for the alteration in calcium metabolism in chronic uremia (p. 89)

Even in healthy individuals, large amounts of phosphoric compounds may exert an unfavorable influence upon the absorption of calcium. During wartime in Great Britain, whole wheat bread was the only kind of bread available. The outer layers of unmilled wheat contain large amounts of phosphorus-rich phytin. The austere war diet was very low in calcium. In the intestine, the formation of large amounts of calcium phytate was sufficient to prevent satisfactory absorption of calcium from the intestine and to cause hypocalcemia. Nowadays, large amounts of phytic acid are given to patients with renal stones. The hypocalciuria ensuing from the ingestion of phytic acid decreases the tendency for renal stone formation.[19]

In most kinds of fatty diarrhea, not only fats but also fat-soluble substances, such as vitamin D are lost in the stools. This impairs calcium absorption from the intestine (p. 40) In addition, large amounts of fatty acids, present in the intestine of patients with steatorrhea, are excreted as calcium or magnesium soaps. Due to the combined action of these two factors, fatty diarrhea of long standing usually leads to hypocalcemia and hypocalciuria.

When large amounts of oxalates are present in the food, insoluble calcium oxalate, which cannot be absorbed, is formed in the intestine. Spinach is notoriously high in oxalates but fortunately also contains considerable quantities of calcium. In certain brands of spinach excessive amounts of oxalic acid (up to 1 1 grams of oxalic acid per 100 grams of spinach) are found. When large quantities of such spinach are ingested, the intestinal absorption of calcium may well suffer

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Chapter 2

Semantics of Bone Diseases

ROENTGEN EXAMINATION OF PATIENTS with different diseases of the skeleton often reveals that the calcium content of the bones is markedly diminished. Since x ray pictures of the bones can only reveal the presence of radiopaque substances, the roentgenologists designate all these conditions as decalcification or, sometimes, demineralization.

Although from a roentgenologic standpoint the term decalcification is correct, this designation has a special meaning for both the bone physiologist and pathologist. In their terminology decalcification indicates that solely calcium is absorbed from bone, but that the bone matrix remains intact. In past decades this condition was known as halisteresis. Nowadays, however, it is generally believed that for all practical purposes halisteresis does not exist.[4] In other words, when the roentgenologist discovers that the calcium content of the bone is significantly decreased, then, as a rule, a considerable part of the bone matrix has also been resorbed. This is the reason that the roentgenologically correct term decalcification has been replaced in most of the nonroentgenologic literature by the term "resorption of bone." The latter designation removes the suspicion that the author might still believe in halisteresis. The term decalcification may possibly be used in discussing the pathogenesis of rickets and osteomalacia. In these conditions the bone matrix is normal, but the calcification is defective. In the same way the radiologist who observes signs of repair of the skeleton uses the term recalcification. The physician however would do well to designate this improvement "reossification" or "bone repair."

Albright has distinguished different skeletal conditions in which bone resorption is a prominent feature.[1] No bone can be formed unless at first the bone matrix, i.e., osteoid, has been laid down by osteoblasts. Ossification of the osteoid then takes place by the deposition of microcrystalline hydroxyapatite in the bone matrix. Therefore, diseases of the skeleton which are accompanied by a lack of calcium (as visualized on the roentgen photos) may be due to any one of the following conditions

1. Excessive resorption of bone by osteoclastic hyperfunction.
2. Primary changes in mineral metabolism.
3. Insufficient formation of bone matrix.
4. Proliferation of normal or abnormal bone marrow elements.
5. Congenital anomalies.

The following points must be kept in mind at all times

1. Excessive and rapid bone resorption due to osteoclastic hyperfunction may be caused by hormonal influences, such as hyperparathyroidism and hyperthyroidism, or by chronic acidosis due to uremia, or they may be of unknown origin, as in Paget's disease. Regardless of the cause, rapid bone resorption always gives rise to a replacement of the normal cellular bone marrow by fibrous tissue, i.e., *osteitis fibrosa*. This fibrous replacement of bone marrow and cancellous bone is only a sequela of rapid resorption of bone, and as such it should be considered *merely* an important sign. It is not a disease entity in itself, just as fever gastric achlorhydria or anemia are no longer considered separate disease entities.

2. *Osteoporosis* is the result of an insufficient formation of bone matrix, usually caused by a disturbance in protein synthesis. When no bone matrix is available, no bone can be formed.

3. Even if there is adequate formation of

bone matrix, there may be no calcium and phosphorus available for ossification. This condition is designated *rickets* in children and *osteomalacia* in adults. In these diseases the bone trabecules are surrounded by non ossified bone matrix which, in histologic sections, presents itself as osteoid zones. In this condition even a purist could not object to the use of the term decalcification or insufficient calcification.

4 The physiologic bone resorption that takes place every day the so-called daily wear and tear of the skeleton, may be diminished due to decreased osteoclastic function. When the usual amount of bone is not resorbed, the normal accretion of bone substance continues and osteopetrosis develops.

5 The proliferation of normal bone marrow elements in congenital hemolytic anemia or of abnormal marrow elements in lymphomas, myelomatosis and leukemias may cause resorption of bone substance. In leukemia, part of the proliferating abnormal reticulum cells may differentiate into fibroblasts rather than leukemic cells. The formation of connective tissue fibers then leads to myelofibrosis. When these connective fibers calcify so-called myelosclerosis ensues. This is frequently seen in disease entities closely related to leukemia (p. 153) but is rare in true leukemia.

6 Hypovitaminosis (C and D) and hypervitaminosis (A and D) may influence the normal development of the skeleton.

7 Congenital anomalies of the bone forming mesenchyma allegedly lead to osteopsathyrosis or fragility of the bones, to polyostotic fibrous dysplasia and to other syndromes.

The diagnostic significance of careful roentgenographic examination of the skeleton can hardly be sufficiently emphasized. Nevertheless, the limitations of the x ray methods must be clearly realized at all times.

Changes in the density of the roentgenograms of bone become evident only when surprisingly large quantities of bone salts have disappeared or have been added. Remarkably enough, it has been demonstrated in careful experiments that 25 per cent of the calcium content of the phalanges of a finger and perhaps even 60 per cent of the bony substance of a vertebra must disappear before roentgenographic evidence of this loss of bone becomes demonstrable.[3] A vertical hole, 14 millimeters in diameter drilled in an excised lumbar vertebra filled with water can hardly be visualized by roentgen examination. Such a hole, present in a living vertebra within the body will certainly be invisible on a roentgenogram, due to the added obscuring effect of the overlying soft tissue.[3] This signifies that a disease may produce considerable resorption of bone yet, no significant evidence of decalcifiation may be elicited by roentgenographic methods. The reverse is also true, and although roentgenograms made at regular intervals may not reveal marked accretion of bone salt, the repair of bone may have been extensive. Realization of this highly unsatisfactory state of affairs has been the reason that for years experiments have been going on to determine roentgenologically the *actual* calcium content of bones. For this purpose, modified densitometers and modern computation equipment are being used.[4] The very latest publications seem to indicate that at least partial success has been obtained. Thus, the hope seems justified that in the future it may become possible to observe increased bone deposition soon after effective treatment of the malady of the skeleton has been initiated.

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Chapter 3

Osteoporosis

Osteoporosis or atrophy of bone, can be defined as a condition in which the production of bone matrix is insufficient. In order that bone matrix be formed the protein metabolism must be normal. As soon as the synthesis of protein in general and of collagen in particular is reduced, the material which the osteoblasts require for the formation of new bone is no longer available. In the absence of bone matrix the formation of new bone is hampered, because bone salts can be deposited only when bone matrix or ground substance is present.

At all times it must be realized that continuously slow steady resorption of bone takes place from all surfaces of the skeleton, more apparent in the spongiosa than in the cortex. This is the daily wear and tear of the bones, which is balanced by daily new formation of bone.[18] In the presence of this continuous daily wear and tear, impaired synthesis of collagen, leading to decreased formation of bone matrix, must have a pernicious influence upon skeletal structures. When the anabolism of protein suffers the bone trabecules decrease in number size and diameter The abnormally slender bone trabecules have a smooth surface. In other words, the osteoid zones representing the bone matrix and surrounding the thinned trabecules are very narrow [22] Osteoblasts are often scarce and there are few signs of osteoclastic activity Follis, studying the osteoporosis in Cushing's disease, did not find any osteoid zones or osteoclasts at all.[9] This atrophy of bone due to insufficient protein production is designated osteoporosis. Such osteoporotic bones are likely to be compressed or fractured under influence of relatively small traumas. This decreased resistance is due to the gross structural arrangement of the osteoporotic bone. In the normal spongiosa, strong bone plates form a regular network with relatively small meshes and it is this structure that is responsible for the remarkable strength of bone (p. 8) In osteoporosis, this strongly built lattice is replaced by a spiderweb-like arrangement of shrunken, thin bones plates, resulting in a gossamer like spongiosa. The changes of the cortex of the osteoporotic bones can best be studied in the terminal plates of the vertebrae. The latter are much thinner than normal, and even by gross inspection the abnormal porosity of the atrophic plates can be recognized.

There are various conditions which may lead to the development of osteoporosis. Anomalies of the protein synthesis of the body are often endocrine in nature. Thus, osteoporosis is a frequent occurrence in different glandular conditions, e.g., in the menopause and in Cushing's syndrome, regardless whether the latter is due to hyperfunction of the adrenal cortex or prolonged administration of corticosteroids. Osteoporosis will also develop when the function of the osteoblasts is impaired. Osteoblasts, the cells that actually produce the bone matrix, are stimulated by the strains and stresses to which the skeleton is exposed under normal circumstances. During immobilization, these stresses are absent and a depression of the function of the osteoblasts will result. Thus, immobilization will necessarily lead to insufficient formation of bone matrix and, subsequently, to osteoporosis. Finally, the synthesis of bone matrix may be quantitatively sufficient, but qualitatively abnormal. In this respect it is significant that ascorbic acid is necessary for the final stages of the formation of collagen fibers. In avitaminosis C, the production of the characteristic collagen fibers suffers and,

consequently, the bone matrix must be abnormal in structure. This explains why osteoporosis is one of the characteristic findings in scurvy

For practical purposes the most frequent conditions under which osteoporosis develops may be summarized as follows

1 In the menopause.
2 In senility
3 In Cushing's syndrome.
4 During ACTH and cortisone treatment.
5 In acromegaly
6 In avitaminosis C.
7 During immobilization

POSTMENOPAUSAL OSTEOPOROSIS

Extensive resorption of bone, affecting a large part of the skeleton, is very frequently observed in women after the menopause. The same disease is a rarity in males. Many statistics published in the past have elucidated this experience. Anderson, for instance, reported that there were 243 women among 289 patients with osteoporosis between 40 and 60 years of age.[3] Cooke[7] mentions that among 800 published cases of osteoporosis, the proportion of female to male patients was 6 to 1 In our experience, the prevalence of this disease in the female is much greater It seems highly probable that in most cases the diagnosis of osteoporosis due to the menopause in males is erroneous. The larger number of these patients are actually suffering from myeloma, malignancies, osteomalacia, renal tubular dysfunction, Gaucher's disease, etc.

Postmenopausal osteoporosis develops not only during the normal menopause, but also after surgical removal of the ovaries and after roentgen castration. In this part of the world postmenopausal osteoporosis is a frequent systemic disease of the skeleton, although it is not as common as Paget's disease.

INFLUENCE OF ESTROGENS AND ANDROGENS UPON THE SKELETON

There is considerable experimental evidence that estrogenic hormones influence the condition of the skeleton. In both female and male pigeons administration of estrogens causes hypercalcemia and osteoblastic stimulation, resulting in increased density of bones. During the egg laying period the serum calcium of pigeons rises to 20 mg per cent, while the serum calcium of chickens rises to values even as high as 100 mg per cent. Primarily, the non ultrafiltrable part of the serum calcium is increased. All this is evidently connected with the appearance in the serum of a phosphate rich lipoprotein which can bind considerable quantities of calcium.[24] In addition, the serum phosphorus of the egg laying hen increases to twice the normal value. Before the eggshells are formed, huge calcium reserves are stored in the skeleton. This calcium storage presents itself in the form of hyperossification of the long bones, where the marrow cavity becomes almost obliterated by proliferating cancellous bone. When the egg laying period is over the excess bone is again resorbed and the phosphate-rich lipoprotein of the serum disappears.

It must be stressed that increase of bone formation under influence of estrogenic substances differs in different animal species. There are even differences among different strains of the same species.[34] Whereas in most mouse strains treatment with estrogens leads to marked proliferation of bone in the extremities, in other strains such excess endosteal bone formation is absent.

Estrogens do not cause new formation of bone in rats. However, the ultimate result is the same, because in rats estrogenic substances prevent resorption of the spongiosa in the metaphysis. Contrariwise, injections of estradiol inhibit skeletal growth in young pigs. Only after several weeks of estradiol administration is the growth process activated again. For the sake of completion it must be added that in all female rodents, estrogens cause resorption of bone in the pubic symphysis and thereby sensitize the pelvis to the

action of relaxin. MacLean and his associates have shown that estrogen labeled with C^{14} is deposited in the skeleton, especially in the reticulum cells of the connective tissue of the bone marrow which is continuous with the endosteum.[18]

Androgens also influence the condition of the skeleton. Although different animal species react differently, male hormone potentiates the action of estrogens upon the skeleton in pigeons and in humans.

As far as human pathology is concerned, it seems highly probable that in women bone formation is inhibited by the decrease of estrogen production that occurs in the menopause. Albright and his associates have demonstrated that in humans injections of testosterone propionate cause positive nitrogen calcium, phosphate, sodium, and potassium balances.[1] Body weight and muscle mass increase. After cessation of this treatment, the positive calcium balance persists for a considerable time, while the excretion of phosphate and nitrogen immediately returns to the levels observed before the treatment period. Administration of either natural or synthetic estrogenic substances also produces a positive calcium and phosphorus balance but does not lead to nitrogen retention. When a maximum effect on the calcium balance has been achieved by estrogen administration, androgen treatment causes still further increase of the positive balance. Due to the positive nitrogen balance, testosterone causes an increased production of bone matrix.

ETIOLOGY

It is generally accepted in our country that the retardation of the protein synthesis, resulting from the estrogen withdrawal in the menopause, is the cause of postmenopausal osteoporosis. This hormonal theory has received preference over older theories that emphasized the influence of laxatives and achlorhydria[6] upon the development of osteoporosis. Groen and his associates have brought out that women with menopausal osteoporosis are often food faddists whose calcium and vitamin D intakes have been low for many years.[13] These authors, therefore, are of the opinion that osteomalacia must play a role in the etiology of the atrophy of the skeleton, which is so frequently observed on the roentgen photos of menopausal women. Nordin,[18a] too stresses that a negative calcium balance of long standing may be a factor in the causation of osteoporosis.

This may well be true in Europe, where only milk used for infant feeding is irradiated (p 59), and where the consumption of mi and cream, irradiated or not, is much low than in our country In bedridden Europea patients, avitaminosis D may easily develo in the course of any protracted illness whicl also leads to anorexia. However in our coun try eggs, irradiated milk, cream and ice cream, belong to the most favored foods, and even a minimal intake of these nutrients will assure a sufficient supply of calcium and vitamin D It is difficult to visualize how under these circumstances, anything less than complete anorexia could prevent a sufficient intake of calcium and vitamin D Thus, it seems hardly plausible that avitaminosis D could play an important part in the etiology of postmenopausal osteoporosis in the United States.

CLINICAL SYNDROME

The main subjective complaint of patients with postmenopausal osteoporosis consists of pain, chiefly localized in the ribs and the back. Radiation of the pain along the sciatic nerves into the buttocks and legs is common, and girdle pains are frequently present. The first symptoms often seem to start after an accidental trauma—a false step from the curb, a slip in the bathtub etc. The pains are aggravated by coughing, sneezing, straining at stool, flexion or extension of the spine. This pain pattern depends upon the localization of postmenopausal osteoporosis, which affects mainly the spinal column, the ribs and the pelvis. The rest of the skeleton remains normal, at least at roentgen examination (p 17) Considerable limitation of the movements of the spine and development of a rounded kyphosis or kyphoscoliosis are com-

mon signs. Loss of height is constant, approximation of the lower ribs to the pelvis is frequent. The general condition of these patients is commonly poor. It is rare to meet a woman with postmenopausal osteoporosis who really looks well, since in such a patient the synthesis of the protein has suffered, not only in the skeleton but also in the rest of the organism.

Ultimately the patients become complete invalids, and if effective treatment is not initiated they end their lives as miserable cripples.

BIOCHEMISTRY

Postmenopausal osteoporosis depends primarily upon changes of the protein metabolism and not upon an anomaly of calcium and phosphorus metabolism. It follows that in the majority of patients with this disease the biochemical changes in serum and urine are negligible. Calcium, phosphate and alkaline phosphatase of the serum are commonly normal, although the inorganic phosphate of the serum may be slightly increased.[1] The calcium excretion in the urine is not excessive except in rare cases where a marked degree of osteoporosis develops acutely within a short time. In such situations the resorption of bone proceeds more rapidly and moderate hypercalcemia and hypercalciuria may be seen. Even nephrolithiasis may then develop. However in a majority of patients with postmenopausal osteoporosis, the atrophy of bone is only slowly progressive and calcium, phosphate and alkaline phosphatase of the serum remain normal. The proteins of the blood also remain within normal limits. Only occasionally is the serum albumin slightly decreased.

ROENTGENOLOGIC FEATURES

Roentgen examination reveals that the atrophy of bone in postmenopausal osteoporosis is almost exclusively localized in spine, ribs and pelvis. This does not mean that the rest of the skeleton is completelynormal. On the contrary osteoporosis, irrespective of its etiology is probably a generalized process, although in postmenopausal osteoporosis the skeletal rarefaction is most prominent in spine, pelvis and ribs. In the rest of the skeleton the rarefaction has not proceeded far enough for the loss of calcium to be visualized by radiologic methods.

In the initial stages of generalized bone resorption of the spine, before vertebral collapse sets in small herniations of the intervertebral disks into the vertebral bodies develop. These partial intrusions of the disks are known as Schmorl's nodules (PLATE 1c) after the famous bone pathologist who first described this phenomenon. In the terminal plate of the vertebral body several areas of decreased resistance are present—e.g., in the area of the nucleus pulposus where originally the notochord had been situated. Other areas of decreased resistance are the result of irregularities in the ossification of the terminal plate. As soon as the terminal plate is weakened by resorption of bone substance, parts of the elastic nucleus pulposus may herniate into the vertebral body, and Schmorl's nodules result. The prolapsed nucleus pulposus tissue irritates the bone trabecules, causing sclerosis of bone around the Schmorl nodules to appear. This sclerosed layer prevents a further increase in size of Schmorl's nodules.

A prolapse of part of the nucleus pulposus into the vertebral body occurs not only in the course of resorption of vertebral bone trabecules, but also under influence of trauma. This must be the reason that roentgenologically Schmorl's nodules are found in 13 per cent of all vertebral columns. Schmorl himself found that at autopsy these nodules were present in nearly 40 per cent of the males and 34 per cent of the females.[39]

When the clinical picture of postmenopausal osteoporosis is completely developed, the most striking roentgenologic finding consists of the washed-out structure of the vertebral bodies, with a sharper than normal definition of the superior and inferior plates. In the vertebral bodies the horizontal trabecules are often more severely compromised than the vertical ones, and a vertical stria

tion of the vertical body results (PLATE 6c) This is usually one of the first signs of osteoporosis of the vertebral column, as is very clearly demonstrated in Sisson's study.[38] Schmorl, in his beautifully illustrated classic on the vertebral column defends a different explanation of this vertical striation.[39] He points out that as soon as the bone trabecules are less numerous and thinner than normal, the vascular channels become more visible. Every vertebra has 15 to 18 nutritive arteries which course vertically through the vertebral body In Schmorl's opinion, the vertical striation of the atrophic vertebral body is attributable to a better visualization of the vascular pattern.

Sometimes the bone atrophy is so severe that, except for the terminal plates, the vertebral bodies have the same density as the intervertebral disks.

As is always the case when extensive resorption of bone takes place in the elements of the vertebral column, the deformity of the vertebral bodies of the lumbar spine is different from the changes of the dorsal vertebrae. The soft and decalcified lumbar vertebrae are compressed by the elastic intervertebral disks these disks being expansible, they elongate and become taller than normal. In severe cases the disks are even taller than the vertebral bodies. In the lumbar spine, the elastic nucleus pulposus compresses the center of the vertebral bodies more than the peripheral parts. Ballooning of the intervertebral disks results, which, in the lumbar spine, leads to the formation of so-called hourglass vertebrae or fish vertebrae (PLATE 1a) In the thoracic spine, the greatest pressure is exerted upon the anterior part of the vertebrae, resulting in the formation of wedge shaped vertebrae (PLATE 2a) Ultimately compression fractures of one or more vertebrae develop (PLATE 2a) As is the case in all rarefying conditions of the vertebral column, pathologic fractures are much more frequently encountered in the 11th and 12th thoracic and the 1st lumbar vertebrae than in the other vertebral bodies. The radiation of the pain from the back along nerves is apparently due to pressur roots by compression fractures of

Thus, in any disease where dec of the vertebral spine takes place, S nodules, vertical striation, wedging thoracic vertebrae and formation of h vertebrae in the lumbar spine occur N these phenomena is specific for osteop Exactly the same roentgen picture is in many other diseases with extensive r tion of bone from the spine.

Osteoporosis of the ribs leads to ext thinning of the cortex and roentgenol decalcification of the remainder of the r The same holds true for the bones of pelvis. In contrast to the extreme atrophy bone present in spine, ribs and pelvis, t roentgen picture of the skeleton of the e tremities and the skull remains seemingl normal (PLATE 1d)

In the most severe forms of postmenopausal osteoporosis, where the patient has been bedridden for a long time, changes in the cortex and cancellous part of the bones of the extremities may be observed. This bone atrophy of the peripheral part of the skeleton is mainly due to the results of long standing immobilization (p 26)

In contrast to the findings in hyperparathyroidism, the lamina dura of the teeth remains intact. Lester Cahn has emphasized that severe alveolar atrophy and pyorrhea may develop in young women after an induced menopause.[6] In his opinion, abrupt loss of estrogenic hormone causes the decalcification of the jaw bone. He also found underdeveloped jaws with large areas of red bone marrow in a patient with congenital agenesis of the ovaries. Groen and his associates carefully examined 24 patients with diffuse alveolar atrophy or so-called paradentosis.[13] They concomitantly found in these patients a more or less pronounced osteoporosis of the spine, and therefore considered the presenile form of alveolar atrophy to be a sign of postmenopausal osteoporosis.

DIFFERENTIAL DIAGNOSIS

In general, it must be stated that post menopausal osteoporosis is too often diagnosed. The reason is obvious. In older women with back pain and roentgenologic evidence of partial or complete compression of one or more vertebral bodies, the diagnosis of postmenopausal osteoporosis is commonly made. Unfortunately, the roentgenograms of the spine in menopausal osteoporosis and in multiple myeloma are often nearly identical (PLATE 2a). This may also be the case in hyperparathyroidism, widespread fibrous osteitis in chronic uremia, osteomalacia (PLATE 5b) and Gaucher's disease (PLATE 1b). All these diseases are generalized in character and necessarily affect other parts of the skeleton too. In order to avoid differential diagnostic errors, x rays of skull and extremities should always be made. When, apart from the changes in the pelvis, ribs and spine, extensive deossification also exists in the skull and extremities, postmenopausal osteoporosis can be excluded and the presence of another disease, especially myelomatosis, must be considered.

Even the complete skeletal survey is not always sufficient. There are cases of multiple myeloma in which the roentgenologic anomalies remain limited to the spine and thereby simulate osteoporosis. Therefore, even if at the skeletal survey the deossification proves to be limited to the spine, pelvis and ribs, a bone marrow puncture a search for Bence Jones proteinuria and for abnormal hyperglobulinemia may be indicated. This especially holds true in males, where postmenopausal osteoporosis is remarkably rare. In males, this diagnosis must usually be changed after careful examination.

When a patient with "postmenopausal osteoporosis" suffers a true pathologic fracture of one of the bones of the extremities, the diagnosis has been proved to be erroneous. In one such instance an older woman was under treatment for multiple compression fractures of the spine, allegedly due to post menopausal osteoporosis. One morning, while she was walking on the street, a sudden gust of wind whipped the handbag she was carrying against her forearm causing a pathologic fracture of the arm. This proved, beyond doubt, that the diagnosis of osteoporosis could not be correct, and further investigation revealed the presence of multiple myeloma.

When, in a woman who previously has undergone a mastectomy for a malignancy, generalized bone resorption of the spine with compression fractures of one or more vertebrae develops, the differential diagnosis between postmenopausal osteoporosis and skeletal metastatic disease may be well nigh impossible. Even the last resort of the clinicians—a therapeutic test—cannot be performed, because in both diseases androgen treatment has a favorable effect. In the event the patient remains well for many years, the diagnosis of osteoporosis must be correct. If, on the other hand, some bone lesions in the skull or extremities or malignant lesions in other organs are found, a dissemination of the neoplastic disease must be diagnosed. Sometimes a puncture of the "decalcified" part of the skeleton is necessary to arrive at the correct diagnosis.

TREATMENT

In the treatment of postmenopausal osteoporosis the administration of male hormones plays an important part. The administration of female hormones plays a more modest role. This therapy is based upon the theory that in this condition, insufficient protein synthesis impairs the formation of bone matrix. Male hormone is one of the few available compounds that are able to speed up the protein synthesis and thereby lead to a positive nitrogen balance. Thus, administration of testosterone propionate, usually combined with estrogen, has become the treatment of choice for osteoporosis. The experimental results which form the basis of this treatment have been discussed on pages 15 and 16.

The routine treatment of postmenopausal osteoporosis consists of intramuscular injections of 25 to 50 milligrams of testosterone

propionate, given two or three times weekly With this treatment, nearly all patients with *postmenopausal osteoporosis improve considerably* The pains disappear, the compression fractures heal and many such patients, bedridden for months, can get up and start to move around. After improvement has been obtained, such patients often can walk without too much difficulty In this stage an adequate light orthopedic corset or brace may be of help. The nitrogen retention that results from the testosterone administration often causes gain of weight and strengthening of previously atrophied muscles.

Unfortunately in women in general, but in postmenopausal women in particular the above mentioned doses of testosterone propionate within a few weeks lead to signs of masculinization. The voice becomes husky and hoarse and develops a masculine pitch. Laryngologic examination reveals the vocal cords to be elongated and swollen, with congested blood vessels running the length of the cords. The swelling extends caudally the subglottic surfaces of the cords often become visible. These patients are embarrassed when on answering the telephone they are addressed as "mister" women who have sung in a choir are obliged to resign. There is nearly always an abnormal development of hair growth on cheeks, chin and extremities, occasionally accompanied by *loss of hair* of the scalp. Other complications, such as pruritus, acne and abnormal stimulation of libido occur but are less frequent. Retention of electrolytes may result in edema of the legs.

Even when postmenopausal women treated with testosterone propionate experience a favorable influence on their invalidity and on the pains in the vertebral spine, the complicating masculinization is a continuous source of bitter complaints. *Fortunately* the signs and symptoms of virilism can be mitigated—at least in part—by the simultaneous administration of estrogens. The addition of estrogens to the testosterone propionate is advantageous, because estrogens not only decrease the masculinization, but in addition they have a favorable influence on calcium and phosphorus metabolism (p. 16) Thus, *for the routine treatment of* postmenopausal osteoporosis, the thrice weekly intramuscular injections of 25 to 50 milligrams of testosterone propionate are combined with an oral dose of 1 to 5 milligrams of diethylstilbestrol or 0 05 milligram of Estinyl or any other natural or synthetic estrogen. The dosage of estrogens has to be varied from case to case. Shorr's recommendation to give 1 milligram of estradiol benzoate for every 30 milligrams of testosterone propionate injected represents a safe baseline.[24]

It must be emphasized that the peroral administration of methyltestosterone in the customary doses of 5 milligrams twice daily has no therapeutic effect in postmenopausal osteoporosis. Physicians who have been disappointed by the results obtained in treating this disease with testosterone preparations, have usually limited their therapeutic efforts to the oral administration of small quantities of methyltestosterone. Large doses of methyltestosterone, as used by Albright for experimental purposes, actually do have a favorable influence upon the osteoporotic skeleton.[3] Unfortunately after administration of such large quantities of the methyl compounds a toxic hepatitis may develop We have always adhered to the routine of administering the androgens *in the form of testosterone propionate* in intramuscular injections, which may be one of the reasons we are well satisfied with the androgen treatment of postmenopausal osteoporosis.

For several years the clinicians have been waiting for a testosterone derivative which actively increases the synthesis of protein without causing masculinization. It would seem that the recently introduced peroral compound *Nilevar fulfills these requirements.*

Of great importance are the investigations of Shorr[22] It has been known for a long time that strontium follows the same metabolic patterns as calcium. Strontium also acts similar to calcium in influencing blood clotting, cardiac contraction and irritability of nerves.

Shorr has offered evidence that ingestion of strontium lactate in daily doses of 7 grams—that is, 1.8 grams of strontium—increases the storage of calcium in patients with postmenopausal osteoporosis with or without simultaneous testosterone propionate treatment. In patients who could not be brought into a positive calcium balance by the administration of calcium alone, the addition of strontium to the diet improved the storage of calcium in the skeleton to such a degree that the calcium balance became positive. Simultaneously, considerable amounts of tristrontium phosphate were deposited in the skeleton.

The influence of dietary treatment on postmenopausal osteoporosis is uncertain.[4] In three patients with osteoporosis, injections of serum protein raised the level of serum albumin and at the same time decreased the calcium excretion in the urine. It seems doubtful that ingestion of albumin by mouth has the same favorable influence. Nevertheless, there can be no harm in prescribing a high protein diet to patients with osteoporosis. In bedridden patients with this disease, ultraviolet radiation or ingestion of vitamin D (10,000 units daily) may well be advisable to improve the intestinal absorption of calcium to optimal levels.

For several years it was generally accepted that even in cases of postmenopausal osteoporosis, where the results of androgen-estrogen treatment had been clinically favorable, roentgenographic evidence of the improvement of the skeleton could not be ascertained. Gradually, this opinion has changed.[29,30] Albright reports that "the recent films of several of the longest treated cases are fairly convincing."[1] Pollishuk and Kleinhause[29] also have seen roentgenologic improvement. Recently, Cooke has published roentgenographic pictures which leave no doubt that the calcium content of the vertebrae had increased considerably after testosterone treatment.[7] Cooke correctly emphasized that two years of treatment will probably be required before improvement of the x-ray changes can be visualized. Schüpbach[31] had occasion to study bone biopsies performed on a patient with postmenopausal osteoporosis before and after androgen treatment. After treatment, the diameter of the bone trabecules had not increased, but the trabecules were covered by long and extended lamellar haversian systems. From this histologic picture the pathologist concluded that a considerable new formation of bone had taken place. No swelling of osteoblasts or development of osteoid seams could be observed. Sherman[32] also saw histologic improvement of the bone structure in a biopsy performed after a four week period of androgen treatment.

SENILE OSTEOPOROSIS

Study of a collection of 4000 skeletons has led to the conclusion that the total skeletal weight increases until the age of 25 to 30 years, at which time it decreases till the age of 45. Thereafter, for an average of 10 years, the weight of the skeleton increases again. This somewhat remarkable resumption of weight gain after the age of 45 years is the result of abnormal bone proliferation due to osteoarthritis—a disease which befalls nearly every person above 45 years. The proliferation of the bone around the involved articulations masks and even overcompensates the influence of the progressive osteoporosis of age upon the weight of the skeleton. Then, after the age of 55 years has been reached, the skeletal weight steadily goes down without any favorable interruption.[16] It is rather discouraging to realize that a pathognomonic sign of senility—senile osteoporosis—sets in as soon as the age of 30 years has been reached. This may be a warning to the older men who notwithstanding the increasing brittleness of their skeleton, continue to indulge in such strenuous physical efforts as competitive tennis, running, ice skating, cycling, water skiing, etc.

The frequency of senile osteoporosis has

been well illustrated by the studies of Gershon-Cohen and associates. Radiologic examination of 136 ambulatory residents of a "Home for the Aged," who were between 63 and 95 years old, revealed symptomless fractures due to osteoporosis in 11 of 54 male inmates and 24 of 82 women.[11] The fractures were most frequently localized in the 12th thoracic and the 1st lumbar vertebra, which again illustrates the vulnerable position of the lower dorsal and the upper lumbar vertebrae. Multiple fractures were often present. The authors emphasize the significance of the absence of clinical symptoms in the osteoporotic fractures of vertebrae in the aged. They conclude that the clinical picture of a fracture of the spine in younger patients is evidently more acute in character than it is in old age.

Senile osteoporosis, which develops in both sexes above the age of 60 occurs also much more frequently in women than in men, which indicates that even in these high age groups estrogen insufficiency still plays a role. The prevalence of senile osteoporosis in women proves that the combination of postmenopausal and senile osteoporosis damages the production of bone matrix much more than senile osteoporosis alone. In other words, if a male and a female above the 60 year level both suffer from the same degree of senile osteoporosis, the female patient will develop clinical symptoms and signs long before the male, because she suffers from concomitant postmenopausal osteoporosis. This is clearly demonstrated by the fact that the notoriously common fractures of the femur neck in older people occur three times more frequently in women than in men. This difference—which must be due to subclinical osteoporosis—is significant since, if anything, men are more exposed to traumas than women. Thus, many clinicians are of the opinion that there is little clinical and roentgenologic difference between senile osteoporosis and postmenopausal osteoporosis.[17] For obvious reasons, the disappearance of the horizontal trabecules of the osteoporotic vertebrae is also present in the initial stages of the senile form.[17]

Senile osteoporosis is treated in the same way as postmenopausal osteoporosis.[3] In both diseases the protein synthesis declines, impairing the deposition of new bone matrix. In senile osteoporosis, too improvement of the deficient formation of bone matrix must be obtained by androgen-estrogen administration.

OSTEOPOROSIS IN CUSHING'S SYNDROME

In Cushing's syndrome hyperfunction of the adrenal cortex exists. This hypercorticism is due either to an adenoma of one of the adrenals or to bilateral hyperplasia of both adrenals. Only in exceptional cases of this disease has a basophilic adenoma of the anterior lobe of the pituitary been encountered. Cushing's syndrome is much more common among females than males. The rarity of the occurrence of this disease in men is well illustrated by the observation that children are even more frequently affected than males. The hyperfunction of the adrenals leads to the production of an excess of 11 oxygenated steroids. These substances the so-called glucocorticoids, favor the transformation of protein into carbohydrates and, at the same time, decrease the synthesis of protein. In recent years, the possibility that adrenocortical steroids may also cause changes in the skeletal ground substance has been considered by several writers.[23]

Most of the signs of Cushing's syndrome are the sequelae of the hypercorticism existing in this condition. The moon-face, the accumulation of fat, especially involving neck and trunk, the atrophy of the musculature of the extremities, the reddish-blue striae, the hypertrichosis, the hypertension, the tendency to edema, the hyperglycemia, the polycythemia, the glucosuria and the increase of the sodium content of the serum can all be explained by the secretion of excessive amounts of 11-oxygenated steroids.

Since, in this condition, the synthesis of protein is impaired, the production of bone matrix must also be diminished. It is no wonder that atrophy of bone is a fairly constant occurrence in Cushing's syndrome. The resulting skeletal disease is grossly and microscopically[9,18] nearly identical with the symptoms and signs which have been described under the heading of postmenopausal osteoporosis. The marked atrophy of bone is mainly limited to spine, pelvis and ribs. Kyphosis and diminuation of stature are nearly constantly present. The vertebrae become less radiopaque and show vertical striation, the terminal plates stand out, the intervertebral disks are taller than normal, and, in the later stages of the disease, wedged and hourglass-shaped vertebral bodies with multiple compression fractures can be visualized on the roentgenograms.[20,21] As opposed to the localization of the bone involvement in postmenopausal osteoporosis, in Cushing's syndrome the skull is frequently affected. The bone atrophy in the calvarium usually shows a patchy distribution and is largely localized in frontal and parietal bones. Triangular or ameboid-shaped areas of bone resorption with ill-defined margins can often be visualized.

Androgen treatment improves the damaged protein synthesis in Cushing's syndrome and thereby favorably influences the osteoporosis, which so frequently occurs in this disease. Experimental evidence indicates that the beneficial action of androgens in Cushing's syndrome depends upon the neutralization (not prevention) of the deleterious effect of 11-oxysteroids on protoplasm. In modern times, surgical treatment of Cushing's syndrome has become the therapy of choice. After removal of an adrenal adenoma or removal of both hyperplastic adrenals, the condition of the patient rapidly returns to normal following administration of adequate quantities of corticosteroids, and the skeletal atrophy completely disappears.

OSTEOPOROSIS DUE TO CORTICOSTEROID TREATMENT

All patients who are treated with corticosteroids for longer than a few weeks develop signs of hypercorticism. Consequently, prolonged oral or parenteral treatment with cortisone, hydrocortisone, meticorten, etc., and parenteral administration of ACTH usually lead to a moon-face, hirsutism, hypertension, acne, hyperglycemia and glucosuria, sodium and water retention—in short, to a complete Cushing's syndrome.

As is the case with the glucocorticoids of Cushing's syndrome, corticosteroids favor the transformation of protein into carbohydrate. Thus, during corticosteroid treatment less protein will be available for the formation of bone matrix. Osteoporosis, leading not only to pathologic fractures of vertebrae and ribs but also to resorption of bone from the calvarium, is just as frequent after prolonged corticosteroid administration as it is in Cushing's syndrome.

Experimentally, cortisone in rabbits clearly inhibits osteoblastic bone activity but does not interfere with the osteoclastic activity.[27] Under these circumstances osteoporosis must necessarily ensue. At the same time, the osteoblastic bone formation in the callus of experimental fractures is inhibited.[24] In the rat, the influence of cortisone on the skeleton is less constant.[19]

Since 1950, reports of osteoporosis in humans due to long-standing corticosteroid treatment have been appearing in the literature.[22] Osteoporosis develops regardless of the nature of the underlying disease for which the corticosteroid treatment was administered. Pathologic fractures after administration of corticosteroids have been reported in patients treated for lupus erythematosus, pemphigus, rheumatoid arthritis, etc. Recently attention has been given to osteoporosis that develops in asthma patients treated with cortisone.[8] Henneman[15] and associates come to the conclusion that progressive osteoporosis is one of the more serious complications or prolonged corticosteroid

treatment. They found hypercalciuria in the majority of 28 sufferers from chronic asthma treated with corticosteroids. After cessation of the steroid medication, the urinary calcium excretion returned to normal. Estrogens in females and androgens in males reduced the hypercalciuria. In this way, this special danger of corticosteroid treatment can at least partly be compensated.

All this points to the conclusion that prolonged treatment with corticosteroids should, if possible, be avoided in women who have reached the postmenopausal stage. In the event this treatment is deemed necessary for female patients of this age group, the urinary calcium excretion should be tested. The development of hypercalciuria is an indication for simultaneous administration of female hormones. If estrogen treatment is unable to reduce the hypercalciuria to normal, it may well be advisable to stop the corticosteroid treatment.

Later it will be mentioned that corticosteroids diminish the absorption of calciu from the intestine and thereby decrease t hypercalciuria which is present in hypervit minosis D and in Boeck's sarcoidosis (101) This appears to be at variance wi the statement that in women with oste porosis corticosteroids may cause hypercalc uria. This contradiction is more apparer than real, however In the acute osteoporos that develops in older women under th influence of corticosteroids, so much calciu is liberated from the bones that hypercalc uria persists, even if at the same time th calcium absorption from the intestine markedly reduced under the influence c corticosteroids. This explains why the acut osteoporosis of the spine, caused by cort costeroids, leads to hypercalciuria. Only whe the hypercalciuria is due to increased i testinal absorption of calcium, as occurs i hypervitaminosis D and Boeck's sarcoidos does hypercalciuria disappear under influenc of cortisone.

OSTEOPOROSIS IN ACROMEGALY

When an eosinophilic adenoma of the anterior lobe of the pituitary gland develops, an excess of growth hormone is produced. The same holds true when a diffuse proliferation of eosinophilic cells is present in the anterior hypophysis. The hypersecretion of growth hormone leads to gigantism in children and to acromegaly in adults. Many anomalies of the skeleton are found in the latter disease which can be explained as the sequelae of an excess of growth hormone. However, in addition there is always a more or less marked osteoporosis. For instance, the kyphosis, which is a fairly constant deformity in acromegaly is at least partly due to osteoporotic changes. There seems no reason to speculate that the osteoporosis is a direct result of the abundance of growth hormone. However the possibility that in acromegaly the diseased pituitary also excretes too much adrenocorticotropic hormone or ACTH must at least be considered. As mentioned in the previous paragraphs, there is ample evidence that an excess of corticosteroids can caus osteoporosis.

Hypogonadism—a frequent complicatio of acromegaly—could also possibly caus osteoporosis. However hypogonadal osteo porosis develops much more readily i women than in men. Thus, if the osteoporosi in acromegaly is due to a lack of estrogeni or androgenic substances, it can be expecte to be more common in women with acrome galy than in men afflicted with this disease Since this is not the case, hypogonadism i probably not the primary cause of osteo porosis in acromegaly

In hypophysectomized rats, a direct antagonism between growth hormone and ACTH can be demonstrated.[3] An increased ACTH secretion by the diseased anterio pituitary would therefore have a teleologically favorable influence by at least partly neutralizing the dangerous effects of the excess of growth hormone. Every drug or remedy apart from its curative action upon disease,

has always one or more unfavorable side actions. In the same way, the osteoporosis of the acromegalic would then represent the unfavorable side action that complicates the curative influence of the hypersecretion of ACTH in the acromegalic disease.

OSTEOPOROSIS DUE TO AVITAMINOSIS C

INFLUENCE OF VITAMIN C ON THE FORMATION OF COLLAGEN FIBERS

Close connections exist between vitamin C and the formation of connective tissue. In the scorbutic guinea pig, wound healing is seriously impaired. Alteration of the ground substance, decrease of the alkaline phosphatase and impairment of the vascularization are all present at the basis of the poorly healing wounds. The proliferation of the fibroblasts is apparently normal, but no true collagen fibers are formed. It is generally believed that during wound healing in a scorbutic animal, the normally proliferating fibroblasts form a sufficient amount of precursors of collagen. In fact, large amorphous masses of reticular material are found in such wounds. However, vitamin C is apparently necessary for the production of the characteristic collagen fibers from this precursor material.[4] In the absence of these fibers, the tensile strength of the new scar tissue is considerably impaired. Within 24 hours after administration of vitamin C to the scorbutic animal the anomaly of the collagen formation disappears and new formation of normal collagen fibers can be observed.

There are many patients in whom avitaminosis C complicates other nutritional deficiences, especially avitaminosis D. Histologic examination of osteomalacic bone sometimes reveals the presence not only of osteoid seams around the trabecules—due to avitaminosis D—but of osteoporosis as well. The latter anomaly is caused by a complicating avitaminosis C.

CLINICAL PICTURE

Avitaminosis C, or scurvy manifests itself as a hemorrhagic tendency with frequent involvement of the skeletal system.

The premonitory signs of scurvy in adults consist of general fatigue, pains and weakness of the legs. Swelling of the gums sets in and gradually progresses to a septic gingivitis with necrosis. Ultimately, the teeth loosen and fall out. In the meantime, petechiae and subcutaneous hemorrhages develop. Subperiosteal hemorrhages cause considerable pain along the long bones and often the extremities cannot be moved. The scorbutic changes of the gingiva develop only in individuals whose teeth have been preserved, newborns or edentulous adults with scurvy do not suffer from gingivitis.

Infantile scurvy (Barlow's disease) was frequently encountered during the years when infants were fed exclusively with highly sterilized milk. The sterilization was sufficient to kill the heat-sensitive vitamin C. The first symptoms and signs of Barlow's disease consisted of anorexia and marked perspiration, followed shortly thereafter by pains, swelling of the extremities and inability to move (so-called pseudoparalysis). The latter signs stemmed from the development of subperiosteal hemorrhages and were most marked in the femurs and legs. At the same time, hemorrhages of the skin, hematuria and even periorbital hemorrhages occurred.

The disease was hardly ever seen in children under the age of six months.

ROENTGENOLOGIC FEATURES

The presence of subperiosteal hemorrhages is the characteristic roentgenologic sign of scurvy in adults. In the initial stages it is usually difficult to recognize a subperiosteal hematoma on the roentgenograms. Only when organization of the hematoma takes place does the shadow of the subperiosteal accumulation of blood become so dense that it can be diagnosed with certainty.[5] After 10 days calcification of the hematoma sets in which considerably facilitates the radiologic

recognition of this lesion.[33] The first calcification always develops in the periphery of the hematoma in the form of a thin calcific line bordering the swelling. Since the subperiosteal hematomas frequently relapse, several such calcium lines may be formed and, ultimately, the shaft may be surrounded by an onion shell like collection of concentric calcified layers (PLATE 2c). Finally the entire hematoma is transformed into a dense calcified mass. Calcification and even ossification of the hematoma have been observed.

Subperiosteal hematomas develop and follow the same evolution both in children and in adults. In children, additional signs are found in the epiphysis and the metaphysis. The epiphyseal centers are abnormally radiolucent, evidently because of impaired ossification. In contrast, the bone shell surrounding the epiphyseal centers is markedly dense. This contrast between the central part and the outer rim of the epiphysis is very frequently present in scurvy. Unfortunately it is not a pathognomonic sign because it also occurs in other diseases.[33] The terminal part of the metaphysis, bordering upon the epiphyseal disk, presents as a dark dense line; this sclerotic layer, the so-called lattice zone, consists of calcifie lagenous matrix. In contrast, a clea several millimeters in diameter is immediately cephalad to the lattice. clear zone an arrest of the osteoblasti tion with extensive proliferation of tive tissue takes place.

Epiphysiolysis—separation of the ep from the diaphysis—may occur in th stages. At the costochondral junctions bone and cartilage are adjacent, cha ossification develop that ultimately m to a bulbous expansion of the ribs.

Scorbutic osteoporosis, caused by hibition of the formation of normal u fibers, can often be seen on the roen grams (PLATE 2c). Atrophy and thinn the cortex may become so marked th a thin drawn pencil line remains. In th cellous bone, thinning and disappeara the trabecules can easily be visualized.

After the avitaminosis C is healed zontal lines of calcification can be within the metaphysis and for a long ti atrophy of the trabecular structure central areas of the epiphyses remai dent.

OSTEOPOROSIS DUE TO IMMOBILIZATION

Increase in urinary nitrogen excretion is the first biochemical change appearing after immobilization of a fracture in a cast. This is probably due to wasting of muscle, and lasts on the average for one month. In the meantime, however, abnormally large amounts of calcium start to appear in the urine. During the first four weeks 24 grams of calcium may be lost, and less marked hypercalciuria may persist for many months. After mobilization of the patient, the urinary calcium falls rapidly to normal values. Immobilization due to generalized paralytic poliomyelitis may also lead to marked hypercalciuria.

For the explanation of these clinically important metabolic changes during immobilization the following data must be consi It has already been mentioned that normal conditions the so-called daily and tear of the skeleton is balanced by blastic new formation of bone. This what complicated process of everlasti struction and reconstruction of bo responsible for the modification o trabecular structure of the skeleton takes place continuously in the course o The thickness, spacing and arrangeme trabecules depend upon the repair o daily wear and tear. The stimulation o osteoblastic function, necessary for th pair of this continuous wear and te derived from the numerous stresses strains to which the skeleton of a h

individual is subjected during muscular activity. During immobilization, these normal stresses and strains to the skeleton are completely absent, no stimulation of the osteoblasts takes place, and no new bone matrix is formed. Thus, when an extremity is immobilized in a cast, the osteoclastic bone resorption continues, but the osteoblasts of the inactive limb no longer produce bone matrix. Insufficient reparation of the osteoclastic loss of bone substance, due to the daily wear and tear, must ultimately lead to atrophy of bone, that is, to osteoporosis of the immobilized limb.

It should be emphasized that the atrophy of disease develops very quickly. This rapid atrophy can hardly be explained by the absence of stresses and strains *alone*. It seems highly probable that during immobilization, the rate of resorption of bone must also be accelerated. The markedly negative calcium balance present in patients immobilized for fractures favors this view. Moreover, not only the immobilization, but also other processes closely connected with the fracture are the cause of marked metabolic changes. This is clearly demonstrated by the observation that normal subjects immobilized in extensive plaster casts lose much less nitrogen and calcium than fracture patients.[24] Following the modern trend of thinking, it is obvious that this difference can be explained by considering the element of stress evoked by the fracture. This stress will cause excessive production of ACTH by the anterior lobe of the pituitary and thereby lead to a negative nitrogen and calcium balance.

These concepts may well be a modern version of theories which were popular a few decades ago. For years it was considered probable that neurotrophic influences flow from the central nervous system via the peripheral nerves to the skeleton. That cessation of these trophic stimuli may play a role in the causation of atrophy of bone is seen in peripheral paralysis, tabes, syringomyelia, and diabetic neuropathy. Whether osteoporosis after immobilization for a fracture is due only to increased bone resorption, combined with lack of replacement of the daily wear and tear of bone or also, in part, to a change in neurotrophic influences, remains to be seen.

Resorption of bone substance due to immobilization is a much more acute process than postmenopausal osteoporosis. For this reason, alterations in serum calcium and phosphorus in fracture patients are more marked than in the more slowly developing postmenopausal and senile osteoporosis. The more extensive the immobilization, the more extensive the osteoporosis, and thereby the more impressive the changes of calcium and phosphorus metabolism. The younger the individual, the more active the metabolism of the skeleton and the more outspoken the influence of immobilization upon calcium content of serum and urine.[13,40] In young patients with severe poliomyelitis or with fractures that necessitate extensive plaster casts, scarcely any bone matrix is formed and hardly any calcium and phosphorus can be deposited. As a consequence, large amounts of calcium and phosphorus, absorbed from the intestine, float aimlessly in the blood, resulting in marked hypercalcemia and hypercalciuria and, ultimately, in nephrolithiasis.

Younger patients with a pelvic fracture whose treatment involves the use of an extensive plaster cast often develop renal stones, whereas patients with a fracture of the humerus and a small cast rarely show stone formation. Stone formation is similarly rare in patients with a fracture of the femur except when the calcium intake is high. The higher the calcium and vitamin D intake, the greater the amount of calcium absorbed from the intestine and the more readily stone formation will develop during immobilization. Liberal milk consumption may be the reason that in one American military hospital the development of renal stones in soldiers with a fracture of the femur increased

to the abnormally high figure of 7 per cent.

In young fracture patients with extensive plaster casts and also in children who are completely immobilized because of severe poliomyelitis, the deposition of calcium in the skeleton may suffer to such a degree that the hypercalciuria and hypercalcemia may lead *to metastatic calcification with calcium* precipitation in the kidney parenchyma. This widespread calcium precipitation in the kidneys may cause oliguria and even anuria with "chemical uremia." This syndrome can easily be confused with hyperparathyroidism. However in hypercalcemia due to immobilization, the inorganic phosphorus of the blood serum is always increased, while in hyperparathyroidism, it is usually decreased.

When the dangerous complications of acute nephrocalcinosis develop the patient *must* be mobilized, notwithstanding fractures or poliomyelitis. Shorr and his associates have devised an oscillating bed which allows regular and rhythmic movements of patients even during confinement in a large plaster cast or during total paralysis due to poliomyelitis. This oscillating bed causes a considerable reduction of the nitrogen and calcium losses, which *normal* persons suffer when immobilized in a plaster cast.[34] Unfortunately the oscillating bed did not improve the negative calcium metabolism of paraplegic patients.[35] This result again indicates that other factors in addition to the absence of stresses and strains may play a role in the causation of the rapid osteoporosis which constantly occurs during immobilization of patients with fractures or poliomyelitis.

The question is often raised whether androgens could favorably influence osteoporosis *due to immobilization* insufficient callus formation in fractures and other orthopedic problems. It must be repeated that androgens increase the synthesis of protein. In postmenopausal osteoporosis the protein synthesis is impaired and, consequently, the material from which the osteoblasts can manufacture protein matrix is not available. By restoring protein synthesis, androgens provide to the osteoblasts the necessary building stone for bone matrix and thereby favorably influence postmenopausal osteoporosis.

In osteoporosis due to immobilization the protein metabolism of the body is normal. In this instance the osteoporosis is caused by the absence of stresses and strains, which results in a paralysis of the osteoblasts. The latter cells no longer produce bone matrix, although plentiful amounts of protein are available. Androgens have no direct influence upon the function of osteoblasts therefore, increase of synthesis of protein under influence of androgens will neither improve osteoporosis due to immobilization nor accelerate healing of a fracture.

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Chapter 4

Rickets and Osteomalacia

As has repeatedly been stated in the course of the formation of bone, the osteoblasts first lay down a bone matrix consisting mainly of protein and mucopolysaccharides. This is followed by the precipitation of a special form of calcium phosphate, so-called hydroxyapatite, within the bone matrix. In rickets and osteomalacia the formation of bone matrix is normal, but either calcium or phosphorus, or both, are not available for precipitation within this matrix. Each day a small amount of bone substance is resorbed which represents the so-called normal wear and tear of the skeleton. This resorption of bone must be compensated for by the deposition of an equivalent amount of bone substance. If calcium or phosphate are not available for deposition in the bone matrix, then owing to the continuous daily wear and tear, the calcium stores of the skeleton are gradually depleted. Irrespective of the etiology when the normal matrix fails to calcify the resulting bone disease is designated osteomalacia in adults, rickets in children. In both conditions, the noncalcified bone matrix is visible at histologic examination as broad osteoid zones bordering the contours of the bone trabecules.

Already in Virchow's time, when the concept of rickets and osteomalacia as being two different diseases was generally accepted, such dissenters as Pommer later Schmorl, Looser, and others, insisted that the two diseases were identical. These differences of opinion lasted until the discovery of vitamin D Therapeutic studies with this agent soon established that osteomalacia of the adult is the same disease as rickets of the child and adolescent.

Until thirty years ago rickets and osteomalacia due to an insufficient intake of
min D combined with lack of exposu
sunshine, were frequent diseases. Sinc
importance of sunshine and vitamin I
the prevention of these diseases has
recognized, both conditions have be
rarities in the Western part of the w
Nevertheless, even now sporadic cas
rickets and osteomalacia occur—not so i
due to lack of vitamin D and sunshine,
due to loss of vitamin D Considerable l
of vitamin D occur in the course of
forms of steatorrhea (p. 40) In such
the absorption of fats and of fat-so
vitamin D suffers, and typical rachitic
osteomalacic bone lesions become man
despite a satisfactory oral intake of
min D

Gradually it has been understood
rickets and osteomalacia may also occ
patients whose intake and intestinal ab
tion of vitamin D are apparently suffic
In such cases rickets and osteomalacia
the result of a dysfunction of the r
tubules. In this group of diseases a decre
reabsorption of phosphates from the tub
lumen (p. 43) exists, leading to m
hyperphosphaturia. Other forms of tub
dysfunction cause hypercalciuria. Due to
ensuing loss of phosphates and/or calc
insufficient amounts of calcium phosp
are available for the normal ossificatio
the bone matrix. Since osteomalacia ca
by tubular dysfunction does not respon
current therapeutic doses of vitamin D
skeletal anomaly is often designated "vita
D–resistant rickets." This name is not c
pletely correct, since the bone lesions
certain forms of tubular dysfunction ca
favorably influenced by tremendously h
doses of vitamin D (p. 45)

PHYSIOLOGY OF VITAMIN D

In the absence of a sufficient amount of vitamin D the absorption of calcium from the intestinal canal is reduced to a minimum, the fecal calcium excretion is increased and the calcium content of the urine is decreased. In contrast, the phosphorus absorption from the intestine and, consequently, the urinary excretion of phosphorus remain normal. Increasing amounts of vitamin D render the intestinal absorption of calcium almost complete. Positive calcium balances can easily be maintained on low calcium diets if sufficient vitamin D is given.

Consequently, insufficient intake of calcium alone hardly ever plays a role in the causation of rickets and osteomalacia, except in conditions where the requirements of calcium are excessively high, as is the case in pregnancy and lactation.

Dihydrotachysterol (A.T 10 Hytakerol) and parathyroid extract, like vitamin D, increase calcium absorption from the intestine. Under the influence of vitamin D a much larger amount of calcium is absorbed from the intestine than under the influence of parathyroid extract. Hytakerol has an intermediary position. All three substances exert a salutary influence both in hypoparathyroidism and in avitaminosis D In recent years vitamin D has become the most popular medicament for both these maladies. The skeletal changes in avitaminosis D cannot be attributed solely to insufficient calcium absorption from the intestine other physiologic processes are also disturbed.

1 It is often stated that vitamin D, like parathyroid hormone, increases the phosphorus excretion by the kidneys by inhibiting the reabsorption of phosphates in the proximal renal tubule.[9] This rule, however, is an oversimplification and probably holds true only for parathyroidectomized animals, not for animals with intact parathyroids. Crawford and associates recently came to the conclusion that in normal animals vitamin D and parathyroid hormone have opposing actions on the renal tubular reabsorption of phosphate.[11] As a matter of fact, in cases of rickets caused by avitaminosis D, aminoaciduria has been found which disappears after vitamin D administration. This is another indication that vitamin D exerts a positive influence on renal tubular reabsorption (p 43) Finally, it is well established that very large doses of vitamin D will augment tubular reabsorption of phosphate in certain tubular disorders, and will change the hyperphosphaturia of these patients to a normal excretion of phosphates.

The possibility that vitamin D influences the urinary excretion not only of phosphorus but also of calcium, must be considered. In the initial stages of avitaminosis D the serum calcium hovers around 9 0 mg per cent, i.e., at the lower limits of normal. Nevertheless the calcium of the urine dwindles to traces, whereas in normal persons such a low normal serum calcium still causes the excretion of considerable amounts of calcium.

2. The curative action of vitamin D in rickets and osteomalacia may not be limited solely to the correction of the changes of calcium and phosphorus in the serum and urine. Experimental beryllium poisoning causes bone changes that are highly reminiscent of rickets. In such animals the serum phosphorus decreases because of the formation of the nonabsorbable beryllium phosphate salt in the intestine. However the decrease of serum phosphate alone is not the cause of the arrest of enchondral calcification. When, under influence of the administration of vitamin D to animals with beryllium poisoning the hypophosphatemia disappears, the changes in the epiphyseal disks persist. Beryllium evidently exercises an unfavorable influence upon enzymatic processes which are necessary for the ossification of the epiphyseal disks. It seems possible that vitamin D has an opposite action and acts as a catalyzer to the enzymes which are responsible for enchondral ossification.

3 *Finally*, vitamin D also increases resorption of bone.[7] This becomes evident in

hypervitaminosis D, both in experimental animals and in humans.

When the diet of a rat with avitaminosis D does not contain either calcium or phosphorus, the administration of vitamin D raises both the decreased serum calcium and phosphorus levels. Since no calcium or phosphorus is offered with the food, neither of these substances can be present in the intestine. The increase of serum calcium and phosphorus which follows vitamin D administration to the rachitic rat on a calcium and phosphorus-free diet can be caused only by a release of calcium and phosphorus due to accelerated resorption of bone.[64] In addition, ten international units of vitamin D are sufficient to restore the calcium absorption from the intestine of the rachitic rats, but this dose is far from sufficient to increase the serum calcium to normal levels. Finally in young rats kept on a low calcium diet, vitamin D increases the serum citric acid just as promptly as it raises the serum calcium. The citric acid effect is not a side action of the influence of vitamin D upon serum calcium, because the curves of serum calcium and serum citrate acid do not run parallel. Therefore, vitamin D must have an influence upon metabolism independent of its action upon intestinal calcium absorption.

Study with radioisotopes also favors a direct influence of vitamin D upon bone metabolism. Balance studies performed after injection of radioactive calcium to animals with avitaminosis D indicate that in this condition both deposition of calcium in and resorption of calcium from bone are diminished—accretion still more than resorption. After vitamin D administration to rachitic animals, both processes increase—accretion more than resorption. In controlled experiments the rate of accretion of calcium in the femur of the rachitic rat was only 0.05 milligram per hour the resorption of calcium from the bone 0.05 milligram per hour, the net increase therefore being zero. After administration of vitamin D the rate of accretion rose to 0.11 milligram. At the same time the resorption rate increased to 0.09 milligram per hour In this way after treatment with vitamin D the net increase of calcium amounted to 0.02 milligram. In *hypervitaminosis* D, the resorption of bone exceeds the accretion (p 51) Especially in humans, hypervitaminosis D always leads to marked generalized loss of bone substance and to metastatic calcification.

The conclusion seems justified that vitamin D performs the following actions

1 Renders absorption of calcium from the intestine possible.
2 Directly influences enchondral formation of bone.
3 Directly influences urinary phosphorus and calcium excretion.
4 Causes not only calcium deposition but also resorption of calcium and phosphorus from the skeleton.

In osteomalacia and rickets due to avitaminosis D the impaired absorption of calcium from the intestine is the main cause of the skeletal changes. The rachitic changes in the epiphyseal disks can perhaps be partly ascribed to a modification of the enzymatic processes which, under the influence of vitamin D leads to enchondral calcification.

RICKETS AND OSTEOMALACIA DUE TO AVITAMINOSIS D

In rickets, irrespective of the etiology both osteoid zones around the bone trabecules and changes in the epiphyseal disks are found. The disks are abnormally broad and remain open, long after the normal ossification of the disk should have taken place. Due to faulty development of the provisional calcification zone, the metaphyseal margins of the disks are markedly irregular all of which can easily be visualized on the roentgenograms (PLATE 3*a*) Since the epiphyseal disks are closed in adults, the main pathologic changes in osteomalacia are limited to the presence of osteoid zones around the trabecules of the cancellous bone.

In the adult, where all the epiphyseal disks

are ossified, cartilage and bone are still adjacent in the costochondral junctions. It follows that structurally a costochondral junction is comparable to an epiphyseal disk. The proliferation of cartilage in the costochondral junctions of the osteomalacic adult and the ensuing swelling of the sternal endings of the ribs are similar to the changes occurring in the epiphyseal disks of the rachitic child. The formation of a "rachitic rosary" in the osteomalacic patient constitutes a strong point in favor of the identity of rickets and osteomalacia.

Infantile rickets occurs in children below the age of three years so-called late rickets is its counterpart in adolescents. In late rickets the same fundamental changes are found as in the infantile form the epiphyseal disks remain open, the proliferating cartilage increases in size and the provisional calcification zone disappears. At the same time, osteoid seams and decalcification of the bone trabecules are prevalent. Fetal rickets is observed only when the mother suffered from osteomalacia during pregnancy

In view of the paramount diagnostic importance of the finding of broad osteoid zones surrounding the bone trabecules, it is necessary to emphasize the importance of correct preparation of specimens of osteomalacic bone for histologic study It is hazardous to search for these osteoid zones—that is, areas of nonossified bone matrix—in histologic bone sections which have been subjected to prolonged decalcification in strong mineral acid. The possibility that exposure to strong acids could lead to confusing histologic pictures—especially to pseudo-osteoid zones—must certainly be considered. It is preferable to search for the presence of osteoid zones in fresh preparations of cancellous bone without preceding decalcification. For this purpose cancellous bone obtained at biopsy or autopsy is ground in a mortar Tiny spicules of bone are mounted in five per cent silver nitrate solution. The phosphate of the bone causes the trabecules to turn black by the formation of silver phosphate, and under low power magnification the unstained broad osteoid zones of rachitic or osteomalacic bone trabecules can easily be recognized.

The moderate secondary hyperplasia of the parathyroids that has been observed in avitaminosis D deserves special mention. In 1907, Erdheim[19] observed hyperplasia of the parathyroids in three cases of osteomalacia. Later, he found the same hyperplasia of the parathyroids in children with rickets and in rats with experimental rickets. Many authors have been able to confirm these findings both in clinical and in experimental avitaminosis D Chickens fed on a vitamin D–free diet and kept in cages covered by amber glass (which filters out all the ultraviolet rays) develop both osteomalacia and a considerable hypertrophy of the parathyroids. The weight of each of the parathyroids may increase to 53 milligrams, as compared to the average weight of 5 milligrams in normal chickens. Addition of cod liver oil to the diet of these experimental animals, daily irradiation with ultraviolet rays for 10 to 15 minutes and small daily doses of parathyroid extract (p 31) all prevent the parathyroid hyperplasia. It appears highly probable that the hyperplasia of the parathyroids in avitaminosis D is caused by the constantly present hypocalcemia.

In avitaminosis D, hypophosphatemia and normophosphaturia frequently occur The decrease of the serum phosphorus in the presence of normal phosphaturia in avitaminosis D has been interpreted to be a sign of hyperparathyroidism. The hypothetical excess of parathyroid hormone secreted by the hyperplastic parathyroids would inhibit the reabsorption of phosphorus by the convoluted tubules, resulting in normophosphaturia and hypophosphatemia.

In this connection it must be mentioned that ingestion of large amounts of calcium salts by patients with rickets and osteomalacia changes the normal phosphaturia to hypophosphaturia. This anomaly does not occur if large amounts of calcium salts are given to patients with genuine hyperparathyroid

ism. In addition, Crawford and associates[11] ascertained that vitamin D has an antagonistic effect on phosphate reabsorption when compared with parathyroid hormone (p. 31). Thus, in the absence of vitamin D the action of the normal amount of parathyroid hormone may be excessive. The hypophosphatemia in avitaminosis D could therefore be caused by unopposed action of physiologic amounts of parathyroid hormone on the renal tubule.

INFLUENCE OF PREGNANCY AND LACTATION

Osteomalacia is still endemic in the northern part of India, Japan, and many provinces of Northern China, where the poor man's food is low in calcium, not high in phosphorus, and practically devoid of vitamin D. In China, milk and butter are unknown as dietary staples, and eggs, liver, seafood, meat, fowl, and other animal products can be enjoyed only by the well-to-do classes. The main source of calories for the poorer classes of North China consists of cereals—mostly millet, kaoliang (broom corn) and corn—eaten with varying amounts of vegetables. The somewhat better situated people use wheat and soyabean flour with considerable amounts of fresh vegetables.[27] Since vitamin D is present only in animal food, the vitamin D intake of the poor population in North China is practically nil. Furthermore, because of the absence of milk and dairy products the diet is poor in calcium. Around 1940 the average daily calcium intake varied between 200 to 250 milligrams. This is a satisfactory calcium intake for the peasants who for the greater part of the day work out of doors and thereby manufacture a sufficient amount of vitamin D in the skin. Especially in the cities, osteomalacia is much more frequent among women than men, although both sexes follow the same vegetarian diet mentioned above. Household duties keep the women indoors so that their exposure to sunshine is minimal, while the men, particularly of the poorer class work in the open.

Comparable conditions prevailed in other parts of the world. In Kashmir, for instance, the poorest women who worked as boat women never had osteomalacia. Their nutrition was very deficient but since they were exposed to the sunshine during their working hours, they did not lack vitamin D. In the same country, however, osteomalacia was frequent among the women of the well-to-do class who had to stay within the walls of the "seraglio" for the greater part of the day.[24]

Loss of calcium during menstruation, but especially losses of calcium during pregnancy and lactation, constitute a drain on the calcium of the female skeleton. Careful probing in the history of osteomalacic women reveals that the very first attack of the disease, that is, the onset of bone pains, is usually observed during lactation and not during pregnancy. Only the heavy losses of calcium and vitamin D that occur during lactation are capable of initiating the disease. When the calcium stores of the organism have been depleted by a previous osteomalacia, the moderate losses of mineral and vitamin D during the next pregnancy are sufficient to cause a relapse or a deterioration of the disease before lactation starts.

It has already been mentioned (p. 9) that there is ample reason to doubt the conclusions of the nutritionists concerning the daily calcium requirement. It is not at all proved that the daily food *must* contain 800 milligrams of calcium in order to safeguard health. On the contrary, when vitamin D is available, even a small daily intake of calcium amounting to 300 or 400 milligrams, is sufficient to keep the calcium stores of the skeleton intact. Although adults can remain healthy with such a low calcium intake—at least, if the administration of vitamin D is sufficient—this does not hold true for pregnant and lactating women.

When, under normal circumstances, just as much calcium is ingested as appears in the urine and stool, the calcium balance is in equilibrium. During pregnancy however this amount of calcium intake is no longer

sufficient to maintain the calcium stores of the skeleton of the patient, because large amounts are diverted to the growing fetus. Calcium balance studies during pregnancy must take into consideration the fetal needs before a satisfactory requirement of calcium can be calculated. Studies with radioactive calcium have proved that calcium atoms are freely and rapidly transferred through the barrier of the placenta from the maternal to the fetal organism (8[a]). It must be noted that this transport of calcium is accomplished against a gradient: the fetal plasma calcium, especially the ionized moiety, is higher than the calcium content of the maternal plasma. The avidity of the fetal bones for calcium may well be an important factor in the migration of calcium from the maternal to the fetal circulation against this gradient. In this respect it should be mentioned that in the placenta considerable amounts of calcium are present. The following data illustrate these points.

The skeleton of the newborn contains 21 to 23 grams of calcium and 14 grams of phosphorus at birth. In exceptional cases the calcium content has even been found to amount to 30 grams.[244] It has been calculated that in order to keep the maternal skeleton intact the pregnant woman must retain 50 milligrams of calcium daily in the third, fourth and fifth lunar months of pregnancy, 120 milligrams in the sixth, seventh, eighth and ninth months, and 450 milligrams during the tenth month. Other authors have expressed the opinion that the expectant mother during the last three months of pregnancy must retain daily a minimum of 200 milligrams of calcium and 100 milligrams of phosphorus in order to safeguard her calcium stores.

Lactation is a still heavier drain on the calcium stores of the maternal skeleton. The calcium content of human breast milk varies between 25 and 30 milligrams per cent. When, during the first few months of lactation 1000 to 1200 cc. of milk are produced daily, 300 to 400 milligrams of calcium will be lost in the milk. Unless this quantity is replaced the maternal skeleton will be damaged. Whereas during pregnancy the calcium intake must at least cover the quantity of calcium removed in the stool and urine, plus the estimated amount required for calcification of the fetal skeleton, during lactation the calcium intake must cover the calcium lost in urine, stool and milk.

In order to satisfy the needs of pregnant women, a daily intake of 1000 milligrams of calcium is necessary, even in population groups accustomed to a low calcium intake under normal conditions. The lactating woman may need *1 to 2 grams of calcium* daily. In order to absorb these amounts, both pregnant and lactating women, of course, need a sufficient amount of vitamin D.

All this is of major importance, because during lactation large amounts of vitamin D are lost, especially in Oriental countries, where breast feeding is continued for an average of two years. It must be added that in the later months of lactation the losses of calcium and vitamin D are curtailed by the progressive decrease in the quantity of milk produced. Since the calcium balance of any woman with avitaminosis D is negative, even if she is not pregnant or not lactating, pregnancy and—even much more—lactation must have a devastating effect upon the skeleton of the mother whose vitamin D intake is unsatisfactory.

As far as the newborn is concerned, the quantity of calcium offered to the breast fed child is always sufficient, even if the lactating mother suffers from avitaminosis D, since the latter condition does not affect the calcium content of the milk. The calcium metabolism of the breast fed infant depends therefore completely upon the vitamin D content of the mother's milk.

The amount of calcium present in the skeleton at birth varies around 0.7 per cent of the total body weight. This percentage climbs gradually until it reaches 1.6 per cent in the adult. In order to keep the calcium content of the skeleton of the growing infant around one per cent, the breast fed child should retain 170 to 310 milligrams of cal-

cium daily As long as the mother receives a sufficient amount of vitamin D the milk contains adequate quantities of this vitamin and the calcium balance of the infant is strongly positive. Under these circumstances the child retains the necessary 76-82 per cent of the 300 to 350 milligrams of calcium provided with the milk.[7] In such children with a favorable calcium balance, the calcium excreted is eliminated partly via the stool, partly via the urine.

When in North China the mother's milk contains no vitamin D, the infant eliminates all the calcium via the stool calcium is no longer present in the urine, and much less than the daily requirement of 200-300 milligrams is retained every day Rickets must necessarily ensue or what is more frequent, the fetal rickets with which the infant was born remains active.

Until thirty years ago infantile rickets was a very common disease in the western part of the world. During the latter part of the 19th century and the first thirty years of the 20th century when infantile rickets was rampant, the pregnant American and European woman had a satisfactory diet, especially a satisfactory vitamin D intake. In these areas the pregnant mother could provide the growing fetus with a satisfactory vitamin D supply and at birth the newborn had sufficient stores of vitamin D to last for about six months. During that era, cow's milk was the mainstay of the diet of infants who were not breast fed. Cow's milk, which contains large amounts of calcium (1180 milligrams per liter) and nearly as much phosphorus (930 milligrams per liter) is a nutrient that favors calcium absorption only when the milk simultaneously contains vitamin D Fortunately in our country all the milk is vitaminized today In olden times the winter milk obtained from cows which were kept in stables was practically devoid of vitamin D Only in the summer when the cows were out in the meadows, did milk contain moderate amounts of this vitamin. The customary boiling of the milk destroyed most of its scanty vitamin D content, and the diet of the infant was thereby practically vitamin D-free. Infants were usually kept inside, or, if they were allowed in the open, they were so heavily dressed that only the point of the infant's nose was visible. The infants gradually exhausted the vitamin D supply with which they were born and, after six months, signs of avitaminosis D developed in the form of rickets. During the next year or eighteen months, the diet was still restricted and consisted mainly of milk, porridge and other easily digestible carbohydrates. Rickets therefore persisted until the age of two when the children were allowed a more liberal diet and began to romp freely out of doors in the sunshine.

The breast fed European children suffered much less from rickets than children fed with cow's milk. The mother's milk was of course not sterilized and the milk of the mother who had a mixed diet contained sufficient amounts of vitamin D In addition, mother's milk contains only 130 milligrams of phosphorus per liter, compared to 320 milligrams of calcium.

The breast fed European children suffered much less from rickets than children fed is of very little importance for the prevention or cure of rickets. These children who were overfed with cow's milk were, if anything, on a calcium rich diet, since cow's milk contains nearly four times as much calcium as mother's milk. Nevertheless, the children fed with cow's milk and a high calcium, low vitamin D intake developed rickets, while the breast fed infants with a low calcium, high vitamin D intake did not.

At that time the question why rickets started when the child was six months old and vanished one and a half years later seemed unanswerable. Since the middle of the 19th century the treatment of rickets with cod liver oil was generally accepted, and every year tons of this oil were prescribed to children after rickets had developed. In retrospect it seems incredible that until thirty years ago the problem of the prevention of

endemic rickets loomed as an insoluble mystery And yet, any physician who systematically used cod liver oil as a prophylactic remedy could have eradicated this widespread disease!

CLINICAL SYNDROME

The first clinical symptoms and signs of osteomalacia are usually fatigue, stiffness, and pains in the bones. Gradually, muscular weakness, adductor spasm and waddling gait develop The spasm of the adductor muscles, especially evident during abduction of the legs, is ascribed to a reflex mechanism which prevents pain sensation resulting from abduction. The characteristic swelling of the chondrocostal junctions of the ribs, the formation of a so-called rosary has already been mentioned. Ultimately, marked softening of the bones causes deformities of the skeleton. The long bones and the spine lose their normal shape, often resulting in grotesque curvatures of spine and limbs.

In later years the diagnostic importance of the roentgenologic features of osteomalacia has been emphasized, and correctly so Nevertheless, it should be stressed that roentgenologic anomalies develop in a relatively late stage of the disease. Many of the clinical symptoms and signs of osteomalacia may already be present at a time when the roentgenograms of the skeleton are still apparently within normal limits (PLATE 4a) In such cases clinical signs and biochemical anomalies are more important than roentgenologic changes for the diagnosis of osteomalacia.

The first signs of infantile rickets in the western world in children who were about six months old consisted of severe perspiration during sleep and some tenderness of the bones when the child was lifted. The child did not try to stand up and dentition was late. Gradually swelling of the lower parts of the ulna and radius, flaring of the ribs and a nodular change of the chondrocostal junctions, the so-called rachitic rosary (p 33) became evident. Finally a kyphoscoliosis of the lower part of the dorsal and the upper part of the lumbar spine developed, because thus part of the weakened vertebral column sagged in the free space between the pillow and the mattress of the bed.

Deformation of the skull manifested itself by bulging of the forehead and frontal bossing The softness of the bones of the skull led to occipito-parietal flattening, and in the most severe cases of rickets the bones of the skull became so soft that the calvarium could easily be compressed This condition was designated craniotabes. In the less severe cases the child still tried to walk but, due to the insufficient deposition of bone salts, developed bowing of the legs.

With adequate exposure to sunshine, beginning when the child was permitted to crawl or walk in the open, the rickets disappeared as if by magic.

Late rickets announced itself with pains in the legs, dull in character and becoming much worse during walking The first visible sign of rachitis tarda was commonly the development of genua valga, less frequently of genua vara. The degree of genua valga would become so extensive that the patients could ultimately walk only with the help of crutches. In one of our patients the pelvis swung forward with the body with each step in the middle of every step the knees knocked together Swelling of the epiphyseal disks at the lower end of the extremities, especially of the radius and ulna, and a rachitic rosary were usually evident. Ultimately marked deformation of the pelvis developed. Pains in the ribs were a common complaint, especially during exertion and coughing The vertebrae were softened, leading to a gradual decrease in body length and, ultimately to kyphoscoliosis.

BIOCHEMICAL SIGNS

In the absence of a sufficient amount of vitamin D the absorption of calcium from the intestinal canal is reduced to a minimum, the fecal calcium excretion is increased and the calcium content of the urine is necessarily decreased. In fact, in most cases of avitaminosis D the urinary calcium drops to traces. As mentioned before, in avitaminosis

e urinary phosphate excretion remains n normal limits, as long as the phos- u intake is adequate. This makes it y probable that an efficient intestinal ption of phosphorus exists in this disease. ever, when in avitaminosis D the cal- intake is increased to very high values, nonabsorbed intestinal calcium forms quantities of insoluble calcium phos-, which are eliminated in the stool. r these circumstances the excretion of horus in the stool is significantly in- ed and the phosphaturia dwindles to r.

e to the influence of vitamin D on the ion of the kidneys, the first biochemical of osteomalacia often consists of the ce of calcium in the urine of patients, in cases where the serum calcium still within low normal limits, around 9 5 milligrams per cent (p 31)

later stages, avitaminosis D leads to ed decrease of serum calcium. The n phosphate in avitaminosis D is also notwithstanding the satisfactory in- al absorption of phosphates from the tine and the ensuing normal phos- uria (p 34)

e weakening of the bones due to in- d calcification results in an increased ity of the osteoblasts this in turn causes crease of the alkaline phosphatase of the n. The diagnosis of avitaminosis D is m when administration of vitamin D s an improvement of the calcium ab- tion from the intestine within one or weeks. This can easily be demonstrated n increase in the urinary calcium excre and a decrease in the calcium content he stool. It requires considerable time re roentgenologic improvement of the um content of the bones becomes le.

dministration of vitamin D to patients avitaminosis D also causes an increase he serum phosphorus. In part, this may the result of the normal inhibition of action of the parathyroids by the administered vitamin D Another factor is the improved calcium absorption from the stool under the influence of vitamin D administration. When more calcium is absorbed from the intestine, less calcium phosphates are formed in the gut. This in turn leads to increased phosphate absorption.

ROENTGENOLOGIC FEATURES

Since in rickets and osteomalacia no calcium phosphate is available, bone substance that disappears under influence of the normal daily wear and tear is not replaced, and in the long run the bone salt content of the skeleton must decrease. In young children the insufficient formation of trabecular bone is compensated for by new formation of fiber bone, derived from fibrous tissue. The ultimate decrease of calcium content of the skeleton of children with rickets is thereby often relatively slight. Nevertheless, the bone is softened and deformities of thorax and spine frequently occur In the adult, formation of fiber bone hardly ever takes place. There is only limited replacement of the bone, absorbed during the daily wear and tear, and ultimately the roentgenograms reveal a much more extensive decrease of the calcium content of the skeleton in osteomalacia than in rickets.

Osteomalacia

As mentioned above, characteristic roentgenologic signs are often absent in the early stages of osteomalacia. In the course of time numerous secondary bone trabecules disappear and the more resistant large trabecules ultimately stand out so clearly that a coarse reticular structure of the cancellous bone results. When the lack of bone reconstruction lasts long enough, the skeleton may become so poor in calcium salts that satisfactory roentgenograms no longer can be obtained. Collapse of vertebral bodies is a frequent occurrence. The softened and weakened pelvis is indented by the pressure of both femur heads, and a so-called triradiate, wedge, or heart shaped pelvis results (Plates 4*a* and 5*a*) In addition, an increased con-

vexity and crumbling of the sacrum with marked narrowing of the outlet are often present. Patchy bone resorption has even been observed in the skull. As mentioned above, in clinical osteomalacia the skeleton may still contain considerable amounts of calcium, although the bones are already soft, as shown by marked asymmetry of the pelvis and symphysiolysis. (Plate 4a)

In the extremities, the structure of bone cortex and cancellous bone is completely changed. The spongious part of the bone becomes strikingly rarefied. The bone cortex disintegrates into multiple parallel layers of bone, resulting in so-called lamellation of the cortex (Plates 2e and 3b) The weakness of the bone leads to bowing of the extremities and, ultimately, to pathologic fractures. Small fissure like areas of bone absorption can be visualized in the cortex (Plates 2d and 3b) Many authors have insisted upon the importance of these transverse fissures for the diagnosis of osteomalacia. These uncalcified incomplete fractures termed "zones of transformation" by Looser represent noncalcified callus, as others have demonstrated by dissecting such fissures. In recent years these small, ribbon like radiolucent zones have been described by Milkman[39] as "symmetrical fractures starting in the cortex."* European clinicians[34] who studied the epidemic of hunger osteopathy that raged during World War II came to the conclusion that these symmetric fissures—as long as they occur in grossly *normal bone*—are characteristic of the presence of osteomalacia (Plates 2d and 3b) These tiny fractures are localized most frequently in the pubic and iliac bones, medial aspect of the femurs, ribs, and axillary borders of the scapulae.[32] LeMay and Blunt[18] have brought out that these linear lines of decalcification are often found in the neighborhood of arteries. This has been confirmed by Steinbach et al. with the help of arteriographic methods.[2] Since these fissures represent osteoid callus, formed as a reaction to incomplete fractures, they can be observed in many other diseases in which the resilience of the skeleton has been impaired, e.g., in Paget's disease, hyperparathyroidism, Cushing's disease, lipoidgranulomatosis of the bones, etc. However, only in osteomalacia are these ribbon like fissures symmetric and does the surrounding bone cortex appear normal on the roentgenograms.

*Milkman's patient allegedly suffered from vitamin D—resistant rickets, caused by phosphate diabetes (p. 44)

Rickets

The outstanding roentgenographic sign in infantile and late rickets is the delayed calcification of the abnormally broad epiphyseal disks. In patients with late rickets, the disks may still be open at the age of twenty The proliferating masses of cartilage cells and the irregular vascular invasion, situated directly against the epiphyseal ends of the diaphysis of the long bones (the so-called metaphysis), penetrate deeply into the diaphysis (Plate 5a) This produces so-called cupping of the ends of the diaphysis. At the same time, the edge of the metaphysis is frayed and serrated.

The cortex of the bone is thin and poor in calcium. Since broadening of the osteoid tissue around the trabecules is invariably present, the bone structure is often less sharply defined than usual. As in osteomalacia, the remaining trabecules of the cancellous bone have a thicker and coarser appearance than under normal conditions (Plate 5a)

When healing of late rickets occurs under influence of treatment with vitamin D, a calcification line appears in the metaphysis at the level of the provisional zone of calcification. This calcification zone, indicating healing often lies in the middle of the hypertrophied rachitic epiphyseal disk. Relapses of late rickets are frequent. Healing of a relapse leads to the development of a similar zone of calcification in the area of new proliferating cartilage. Ultimately multiple calcium lines result at the ends of the diaphyses—the "annual rings" of rickets.

In the earlier stages of the disease, a decrease of the calcium of the provisional

calcification zones is especially noteworthy In severe cases of rickets, subperiosteal bone formation takes place. In the past, this frequently required a discussion of the differential diagnosis of rickets and congenital syphilis.

Finally, it may be mentioned that the roentgen examination of babies with fetal rickets usually reveals craniotabes and swelling of the costochondral junctions, with suggestive enlargement of the metaphyses of radius and ulna—especially cupping of the diaphyseal ends.[23] Under vitamin D treatment, condensation of bone occurs at the diaphyseal ends of the shafts the ends become more sharply defined and less irregular, and cupping of the ends becomes less deep. The last remaining sign commonly observed is a small narrow zone of condensation, with a slight ground-glass appearance of the metaphyses.

TREATMENT

The results obtained in the past with cod liver oil were highly satisfactory since the latter preparation contains large amounts of vitamin D (and, incidentally of vitamin A) Unfortunately, the treatment was hardly ever given systematically, because it was not understood why cod liver oil had this miraculous influence upon rickets and osteomalacia. This remained a mystery until vitamin D was discovered. In the western part of the world the disagreeable taste of the preparation was another reason that the treatment was often prematurely terminated (at the insistence of the patients) Fortunately the majority of Chinese patients likes the taste of cod liver oil.

Nowadays, 5 000 to 10,000 units of vitamin D and exposure to sunshine or ultraviolet radiation immediately clear up the symptoms and signs of this disease. As a matter of fact, the disease has practically disappeared in our part of the world mainly because of our better understanding of the cause of the disease, and partly because of the addition of vitamin D to some of our nutrients.

This chapter on rickets and osteomalacia serves as an introduction to a discussion of the bone changes observed in long-standing fatty diarrhea and in renal tubular dysfunction.

RICKETS AND OSTEOMALACIA DUE TO FATTY DIARRHEA

Malabsorption of fat-soluble vitamin D is present in many cases of chronic fatty diarrhea. This occurs in the sprue syndrome, in celiac disease, in chronic biliary obstruction, in widespread infiltration of the mesenteric lymph nodes by carcinomatous, tuberculous or lymphomatous, in Whipple's disease —a granulomatous change of these nodes—and, rarely in sclerodermatous and amyloid changes of the intestinal wall. All these diseases must last for more than two years before skeletal anomalies develop. Malabsorption of vitamin D is much less marked in steatorrhea due to long standing obstruction of the pancreatic ducts.

In the sprue syndrome and in scleroderma the absorptive powers of the small intestine are impaired. In chronic biliary obstruction the bile acids cannot reach the lumen of the small intestine. Bile acids act as emulsifiers of the intestinal contents and in the absence of emulsification, fatty substances—also vitamin D—cannot be absorbed. Widespread infiltration of the intestinal lymph nodes by tuberculosis, cancer lymphoma, or granuloma interferes with the transport of fat via the lacteals toward the thoracic duct. In pancreatic disease the absence of lipase prevents the hydrolysis of neutral fats, which is necessary for fat absorption.

Apart from the losses of fat-soluble vitamin D in the fatty stools, patients with long-standing steatorrhea are often too debilitated to expose themselves regularly to sunshine, and no vitamin D is formed in the skin. The combination of malabsorption and lack of formation of vitamin D in sprue, celiac disease chronic jaundice, biliary fistula and

infiltration of the mesenteric glands results in avitaminosis D

In many kinds of fatty diarrhea not only vitamin D but also calcium is lost in the stool, a large part of the stool fats consists of fatty acids, which are eliminated in the form of calcium soaps. It has been reported that in steatorrhea the absorption of calcium can be restored to normal by the administration of moderate amounts of vitamin D, despite the fact that the diet remained unchanged. Notwithstanding the improvement of calcium absorption, the rickets and osteomalacia persisted.[8] This result seems to justify the conclusion that the calcium loss in the stool plays only a minor role in the causation of osteomalacia that occurs in the course of prolonged fatty diarrhea.

Fatty acids are absorbed freely from the lumen of the small intestine, in contrast to neutral fats, which are absorbed only with difficulty In pancreatic disease, the absorption of fats through the intestinal wall remains completely normal but lipase cannot reach the lumen of the intestine. In the absence of lipase no hydrolysis of neutral fats takes place. Since even the normal intestinal wall permits the absorption of only fatty acids, not of neutral fats, the nonabsorbed neutral fats are eliminated with the stools, from which the pancreatic steatorrhea ensues. However, the absorptive powers of the intestinal wall are not impaired and the normal absorption of other fatty substances continues. It follows that vitamin D is absorbed without difficulty Small losses of vitamin D may occur because part of this vitamin is dissolved in the eliminated stool fats.

In pancreatic disease bacterial hydrolysis of neutral fats in the colon may still cause the formation of a relatively small amount of fatty acids. These fatty acids are also eliminated in the stool, since fatty acid absorption takes place only in the small intestine, not in the colon.

The severe rickets commonly present in children with celiac disease[4] sharply contrasts with the absence of rickets in children with steatorrhea due to cystic fibrosis of the pancreas.[11] In the latter disease, often designated mucoviscidosis, the losses of vitamin D, as is true in all instances of pancreatogenic steatorrhea, are insignificant compared to those in celiac disease and sprue.

There is ample experimental proof that in the presence of a biliary fistula with diversion of bile, softening of the bone develops. When the gallbladder of animals is connected with the urinary bladder, all the bile is eliminated in the urine and typical fatty stools appear After a few weeks the first signs of osteomalacia become apparent after sixteen weeks pathologic fractures of the ribs occur and hyperplasia of the parathyroids develops. After reinstitution of the normal path of the bile flow it takes many weeks before the hyperplasia of the parathyroids and the condition of the skeleton return to normal.[36]

Bone changes in humans with chronic biliary fistula or with long standing jaundice have frequently been reported, even in cases where the possibility of senile or postmenopausal osteoporosis can be excluded. During the last few years we have observed[18a] the development of osteomalacia in the following cases

(1) A male, 56 years old, with chronic obstructive jaundice due to a postoperative stenosis of the common duct.

(2) A female, 48 years old, with a biliary liver cirrhosis and chronic obstructive jaundice. This patient had previously been operated on for gallstones.

(3) A male, 46 years old, with chronic jaundice due to a postnecrotic liver cirrhosis.

(4) A female, 47 years old, with chronic obstructive jaundice due to a cholangiolitic liver cirrhosis.

(5) A female, 32 years old, with sclerodermatous changes of the small intestine.

All five patients had steatorrhea.

If the patients are ambulant, difficulty in

walking is the first complaint. In bedridden patients pains in the back which soon become excruciating in character are the first manifestations of osteomalacia. Roentgen examination may reveal compression of one or more vertebral bodies (pp. 38-39) The pains resist all treatment unless the correct diagnosis is made and the appropriate therapeutic measures are prescribed.

In cases of osteomalacia due to fatty diarrhea, the greater part of orally administered vitamin D is excreted in the stool. Therefore, little therapeutic effect is obtained by the administration of 5000 I U of vitamin D as is commonly given in endemic cases of rickets and osteomalacia. Occasionally, very large doses of vitamin D, 50,000 to 100,000 units daily, have a salutary effect. Some authors advocate weekly intramuscular injections of 300 000 units.[9]

Total body radiation with ultraviolet light also gives reliable therapeutic results. The radiation should start with an exposure of two minutes. The time of radiation must be increased gradually until the patients ultimately receive daily ultraviolet treatments of 30 to 60 minutes' duration. With this treatment the bone pains of such patients readily improve, even if the original disease remains incurable. The hypocalcemia and hypophosphatemia often return to normal values. The increased alkaline phosphatase may not decrease, because in patients with liver disease the increase of the alkaline phosphatase depends more upon the biliary obstruction than upon the osteomalacia.

In cases of fatty diarrhea due to a disease of the pancreas, the stool contains an excess of both fat and nitrogen, because neither lipase nor trypsin reaches the intestinal lumen. In these conditions the nitrogen losses may impair the protein synthesis to such an extent that even the production of bone matrix suffers and osteoporosis results.

In late stages of fatty diarrhea due to sprue, biliary obstruction or biliary fistula, the ultimate cachexia may impair protein synthesis. In such cases the loss of fat soluble vitamin D causes osteomalacia, the insufficient production of protein, osteoporosis. The condition of the skeleton of such patients will improve only if the osteomalacia is treated by ultraviolet radiation and the osteoporosis by androgen injections or peroral administration of Nilevar

Another aspect of this problem is emphasized by Ahrens et al., who carefully studied a group of 21 cases of biliary cirrhosis suffering from significant steatorrhea.[1] In 12 patients roentgen examination revealed generalized bone resorption of the skeleton, and 7 patients complained of bone pains. Serum calcium and phosphorus values were not available, but 5 of 6 patients treated with vitamin D experienced relief of pain. The authors felt that osteomalacia was the main cause of the bone changes, but that there was also a certain amount of superimposed osteoporosis. In their study the circulating estrogen levels were found to be low, as judged by the vaginal smear technic. It was thought that a certain degree of osteoporosis may have resulted from this estrogen deficiency, which may well have been connected with the liver damage.

Atkinson, Nordin and Holmes also comment upon the frequent occurrence of osteoporosis in the course of fatty diarrhea.[3] They studied 24 patients with steatorrhea that was due mainly to intra or extrahepatic obstructive jaundice. Seven patients suffered from osteomalacia, two from osteomalacia combined with osteoporosis, three from osteoporosis. Starvation and cachexia, leading to depletion of the protein stores of the body appeared to be the main causes for the development of the osteoporosis. However a few cases remained where the etiology of the osteoporosis could not be explained.

It has been reported that children with congenital atresia of the bile ducts can be kept alive by positioning cannulae in the liver parenchyma, which serve to drain the bile to an extracorporeal reservoir.[81] It remains to be seen whether the administration of vitamin D will permit the skeleton of these children to develop along normal lines.

VITAMIN D–RESISTANT RICKETS AND OSTEOMALACIA CAUSED BY TUBULAR DYSFUNCTION

In most renal diseases, glomerular lesions lead to impairment of kidney function. This holds true for chronic glomerulonephritis, pyelonephritis, arteriosclerotic kidney disease and even for the later stages of myeloma and the amyloid kidney. In cases where glomerular dysfunction leads to long-standing renal insufficiency and acidosis, bone lesions, especially osteitis fibrosa (p. 11), may ultimately result. In uremia due to chronic nephritis, pyelonephritis, etc., tubular dysfunction is also present, but the result of the abnormal function of the tubules is insignificant compared to the electrolyte changes caused by the glomerular disease.

In recent years, a completely different category of renal conditions has been studied in which involvement of the glomerular function is absent or only minimal, but where considerable disturbance of tubular function exists. Such conditions are brought together under the collective title of "renal tubular dysfunctions."[10] In these cases, a remarkable disease of the skeleton, so-called "vitamin D–resistant rickets or osteomalacia," develops.

The functions of the proximal and distal convoluted tubules are different. In the proximal convoluted tubules the reabsorption of the greater part of the phosphates and an almost complete reabsorption of glucose and amino acids takes place. Around 180 grams of glucose are reabsorbed daily and this reabsorption is so efficient that the urine, present in the midportion of the proximal convoluted tubule, is already sugar free.[6] If the reabsorption in the proximal convoluted tubule is impaired, hyperphosphaturia, sometimes combined with glycosuria and aminoaciduria, result. The hyperphosphaturia is so marked that the serum phosphate diminishes. Although the tubular reabsorption of calcium is probably not impaired, hypocalcemia and hypocalciuria are nearly always present, allegedly because in this condition an excess of calcium is excreted in the bowel.

Aminoaciduria is known to occur in other conditions where damage to the proximal renal tubules exists.[13] This has been observed after administration of compounds such as lead, uranium, nitrobenzene, and cresol, which specifically damage the proximal part of the nephron. Aminoaciduria is present in hepatolenticular degeneration, or Wilson's disease. In this malady large amounts of copper are excreted in the urine, and the deleterious effect of copper on the proximal renal tubules is considered to cause the aminoaciduria. In infantile rickets, aminoaciduria also occurs, allegedly as a result of the damage to the renal tubules caused by the avitaminosis D (p. 31).

The function of the distal part of the nephron is completely different. Here, the ultimate concentration and acidification of the urine takes place. The antidiuretic hormone of the posterior pituitary causes the necessary reabsorption of water in the distal convoluted tubule. Acidification is obtained by production of hydrogen ions, which are derived from the carbonic acid of the plasma. In addition, the distal convoluted tubules are the site of ammonia formation. When the function of the distal part of the tubules is impaired, ammonia is no longer manufactured.* In the absence of hydrogen ions and ammonia production, the acid base balance of the body is endangered. Since no ammonia is available, large amounts of sodium, calcium and potassium must be excreted in the urine in order to neutralize the organic and inorganic acids which are the end products of the intermediary metabolism. Marked hypercalciuria and hyperpotassiuria and moderate hypernatriuria result. The loss of these large amounts of fixed alkali via the urine causes a tissue acidosis, diminishing the CO_2 combining power of the plasma. At the same time, the urine is alkaline because no hydrogen ions are liberated in the distal tubules. The disparity between acidosis of the plasma due to a low bicarbonate content, as opposed

*It should be mentioned that many British investigators have another explanation for the defective ammonia production.[32,33]

to the alkaline reaction of the urine, is one of the diagnostic features of this impairment of the function of the distal tubule. The reabsorption of chlorides is not involved—on the contrary, since an inverse relation exists between *reabsorption of bicarbonate and chloride*, the loss of bicarbonate increases the reabsorption of chloride and causes hyperchloremia.

It follows that in all dysfunctions of either proximal and/or distal convoluted tubules, a significant increase of the excretion of either calcium and/or phosphorus is prevalent. Under these circumstances skeletal disease may easily develop. In addition, the dysfunction of the distal tubules often causes calcium deposition in the kidneys, viz., nephrocalcinosis.

Three different forms of renal tubular dysfunction, all leading to so-called vitamin D–resistant rickets or osteomalacia, can be distinguished. For several years there has been a tendency to sharply differentiate between these three entities. It gradually has become evident that in many patients with tubular dysfunctions signs of both dysfunction of proximal and of distal tubules can be elicited.[16] Often slight or moderate glomerular dysfunction is also present.

PHOSPHATE DIABETES

In this syndrome, described by Fanconi and Girardet,[14] the phosphate reabsorption which under normal circumstances takes place largely in the proximal convoluted tubules is impaired. The term phosphate diabetes has been introduced by Fanconi. The word diabetes means "excessive flow", therefore, phosphate diabetes indicates only the presence of hyperphosphaturia. Thus phosphate diabetes is not associated with diabetes mellitus. Nevertheless, due to a concomitant impairment of the tubular reabsorption of glucose, *renal glucosuria may occur in phosphate* diabetes. Marked phosphaturia leads to considerable losses of phosphate and thereby to hypophosphatemia. The alkaline phosphatase of the serum is increased. In most cases of phosphate diabetes the urinary calcium excretion is diminished, because excessive quantities of calcium leave the body via the intestine (p 43). Under these circumstances not enough phosphate is available for normal ossification of the bone matrix. This, in children, must necessarily lead to rickets, in adults, to osteomalacia. In both diseases broad osteoid zones are found; moreover in rickets the epiphyseal disks do not ossify and are abnormally wide.

It follows that both phosphate diabetes and avitaminosis D cause rickets and osteomalacia. In avitaminosis D calcium is not absorbed from the gut, but phosphate is present in normal quantities, whereas in phosphate diabetes not enough phosphate is present for normal calcification although calcium is readily available. The skeletal anomaly which results is the same, but the treatment differs.

About 40 cases of rickets and osteomalacia due to this so-called phosphate diabetes have been reported since 1952.[2] Fanconi himself observed eleven such patients. This condition is a hereditary condition (p 180). The frequency therefore occurs in subsequent generations. Phosphate diabetes does not lead to nephrocalcinosis or nephrolithiasis, because the urinary excretion of calcium is far below normal.

This condition has also been observed in association with neurofibromatosis,[23] another hereditary condition (p 180). The frequent skeletal anomalies in neurofibromatosis, especially widespread resorption of bone, may at least partly be due to phosphate diabetes and not only to involvement of the skeleton by proliferation of the neurilemma of the peripheral nerves.

It has already been mentioned that the original patient of Milkman, who led the latter to emphasize the diagnostic importance of symmetric fissure-like fractures for the diagnosis of osteomalacia, actually suffered *from phosphate diabetes*.

The symptoms and signs and the roentgenologic features of phosphate diabetes are identical to the clinical and roentgenologic syndrome of rickets and osteomalacia caused by avitaminosis D (p 32). However cur-

doses of vitamin D (3000 to 5000 units daily), as used for the treatment of infantile rickets, are not sufficient to decrease the loss of phosphate in the urine, which is the cause of the rickets and osteomalacia in this condition. For this reason, rickets caused by phosphate diabetes has been designated as vitamin D–resistant. This term is not completely correct, since very large doses—50 000 to 100,000, sometimes even 500,000 to 1,000,000 units of vitamin D daily—sufficiently increase the tubular reabsorption of phosphates to improve the bone condition. This may at least partially be explained by the observation that vitamin D activates the alkaline phosphatase of the renal tubules.[18] The latter enzyme, scarcely present in the tubular cells of patients with tubular dysfunction, is necessary for phosphorylation, an enzymatic process without which tubular reabsorption seems to be impossible.

Injections of testosterone propionate may be added to the administration of the large doses of vitamin D Androgenic substances reputedly cause hypertrophy of renal tubules, which might lead to an improvement of the tubular reabsorption, especially of amino acids. It follows that in cases of seemingly intractable rickets, determinations of serum and urinary phosphate and of phosphate clearances can clarify the situation and lead to a correct diagnosis and treatment of Fanconi-Gérardet's phosphate diabetes.

LIGNAC-FANCONI'S DISEASE

In 1923 Lignac [19] autopsied two boys, two and three years old, who during life had shown signs of severe rickets and stunted growth, or dwarfism. Their physical development was poor Both children had albuminuria, the first, "lactosuria." Autopsy revealed the presence of an "albuminous nephrosis" in one child and an acute pyelonephritis in the other At gross examination, large deposits of cystine crystals were seen in spleen, liver and mesenteric lymph nodes. Microscopic examination revealed the presence of cystine crystals in bone marrow, lungs, kidneys, choroidal plexus, conjunctiva, cornea, uvea, sclera and episclera. Cystine was not found in the skin or in the connective tissue of the muscles. The cystine was present either as flat hexagonal crystals or as small rods. Both children had a hydrocephalus. Lignac, emphasizing the metabolic anomalies inherent in this syndrome, named the disease "cystinosis."

Later, Lignac found a third case of cystinosis in a girl of 14 months, who also presented stunted physical development, severe rickets, and renal lesions. In this child not only cystine deposition in the visceral organs, but also a cystine stone in the left renal pelvis and two small cystine stones in the right ureter were found. Lignac ascribed the stunted growth and the other skeletal changes to insufficient protein synthesis ensuing from disturbed cystine metabolism. Since he—and later other investigators—could cause kidney disease by cystine administration to experimental animals, Lignac concluded that the renal changes in the children he described were the sequelae of abnormal cystine metabolism. More and more clinicians agree with Lignac's conclusions.[6,18,85]

In 1933 and 1934, De Toni and Debré, respectively, described comparable cases of rickets and cystinosis. The latter found that in his case the output of organic acids was greatly increased. In 1936 Fanconi,[18] in an article on "Early infantile nephrotic-glucosuric dwarfism with hypophosphatemic rickets," clarified one of the mechanisms which must play an important role in the causation of the skeletal disease of these patients. He found that in this disease hypophosphatemia and hyperphosphaturia were constant signs. He further demonstrated that this anomaly of the phosphorus metabolism was due to a decreased reabsorption of phosphates in the proximal convoluted tubules. Usually, the tubular reabsorption of glucose and amino acids is also impaired. In cases of Lignac Fanconi's disease or cystinosis, unless there is an added dysfunction of the lower convoluted tubule, hypercalciuria does not occur

Fanconi's suggestion that marked amino-aciduria exists in these patients was later con

firmed by chemical analysis by McCune. In extreme cases, the daily urinary excretion of amino acids may go up to 8 grams, that is, 15 to 30 times the normal excretion in adults. It has already been mentioned that in patients with Lignac Fanconi's disease the functional defect of the proximal tubules is often complicated by an anomalous function of the distal tubules. The latter defect leads to loss of base and acidosis.

A special modality of this disease in children who in addition to the Lignac Fanconi's syndrome, have cataracts and severe mental retardation, has been termed by Fanconi the "oculo-cerebro-renal syndrome."[13]

In children with the Lignac Fanconi syndrome, just as in cases of phosphate diabetes, the excessive loss of phosphates in the urine results in a decreased availability of mineral substances for the normal calcification of bone. The ensuing rickets (PLATES 3c and 3d) does not improve with the use of ordinary doses of vitamin D It must be pointed out again, however that very large doses of vitamin D 500 000 units daily have a therapeutic effect and improve the biochemical changes ensuing from the abnormal tubular function. Under these circumstances, closure of the epiphyseal disks and reossification of the weakened skeleton take place.

By 1954 56 cases of this disease had been reported in the literature. In 1952, a review of 21 cases of cystinosis[9] revealed that the disease is familial in origin. It involves a single recessive trait and does not occur in more than one generation of the same family

The first signs of Lignac Fanconi's syndrome are polydipsia, polyuria, and anorexia. The children often vomit intermittent constipation and diarrhea are frequent. Signs of rickets both clinical and radiologic, are always prominent. Glucosuria without hyperglycemia is nearly always present, and ketonuria without ketonemia is frequent.[21] Paper chromatography has shown that about twenty different amino acids may be present in the urine. Hyperphosphaturia and hypophosphatemia are constant signs. The serum calcium usually varies around normal levels the serum bicarbonate is low and the alka[line] phosphatase is high. The disease starts dur[ing] the first or the beginning of the second y[ear] and, because of the anomalous amino ac[id] and protein metabolism, death commonly o[c]curs before puberty Death is caused by inter[current] infections and hyperpyrexia, episodes of muscular weakness and lethargy uremia or vasomotor collapse. Part of the latter mysterious syndrome may be due to hypopotassemia Dent[10] has demonstrated that in some of these cases an abnormally high potassium clearance exists. Photophobia, a result of deposition of cystine in the cornea, is occasionally observed.

Whereas many different amino acids are excreted in the urine, cystinuria occurs o[nly] inconstantly Therefore, this Lignac Fanco[ni] syndrome should be carefully differentiate[d] from the more frequent familiar disease, cystinuria. In the latter condition otherwise healthy persons excrete large quantities of cystine—usually also lysine, arginine, and ornithine—in the urine and form cystine stones in the urinary tract. Patients with true cystinuria have no cystine deposits in the visceral organs, no hyperphosphaturia, no hypophosphatemia, and, consequently do not develop either rickets or dwarfism.

It has been possible to find anatomic and enzymatic anomalies in the tubular apparatus of children who suffered from Lignac Fanconi's disease. In three such cases microdissection revealed that the glomeruli were normal. The proximal convoluted tubules, however were abnormally short and the connection between tubule and glomerulus consisted of a remarkably long and narrow "swan-like" neck.[15] This morphologic anomaly has until now only been found in kidneys of patients with Lignac Fanconi's syndrome.

In the tubules of the kidneys of children with this disease, phosphatase is absent, just as in the case in phosphate diabetes. This favors the assumption that the deficient reabsorption might be caused by insufficient phosphorylation. However absence of phosphatase from renal tubules occurs in many

different renal diseases and is far from specific for tubular dysfunctions.

The diagnosis of Lignac Fanconi's disease can be made when, in the presence of vitamin D–resistant rickets, signs of cystinosis can be elicited. During life, cystine crystals can be found in lymph node biopsies, in microscopic sections of the bone marrow obtained by sternal puncture or in the cornea by examination with a slit lamp It is generally agreed that the hyperphosphaturia must be the result of faulty tubular reabsorption. The ammoaciduria of these patients cannot be explained solely by a disturbance of the renal tubular function, because the amino acid content of the serum in these cases is higher than normal. Fanconi remarks that the decrease of tubular reabsorption of phosphates and glucose must be caused by an anomaly of the enzyme activity which is responsible for the transportation of substances through the tubular walls. In view of the absence of phosphatase in the tubules of the kidneys of patients with Lignac Fanconi's disease, this point seems well taken. The error in enzymatic function is probably not limited to phosphatase or to the kidney tubules, but may also affect the general metabolism of amino acids. As a result, not only is the urinary excretion of amino acids increased but, in addition the intermediary metabolism of amino acids must be disturbed. A considerable amount of amino acids remains unchanged in the body and cystine, which is the least soluble amino acid, precipitates in the reticuloendothelial system. Although, as mentioned above, these patients until recently hardly ever reached the age of 15 years, in modern times the prognosis has become more favorable. Administration of very large doses of vitamin D and careful regulation of the disturbances of the electrolyte balance often prolong the life span of these patients.

The defect of the reabsorption in the renal tubules elucidated by Fanconi explains the vitamin D–resistant rickets and infantilism which are constantly present in this syndrome. Nevertheless, the original idea of Lignac that an abnormal cystine metabolism plays an important part in the etiology of this disease is still valid, even if in a few carefully observed cases no cystine deposits have been found. As a matter of fact, the recent literature mentions that at least part of the abnormalities of the Lignac Fanconi syndrome "are due, not to an inborn error of tubular function, but rather to secondary renal damage, induced by the cystine deposits." The latter statement clearly illustrates that modern investigators[8] return to the original conclusions of Lignac. The deposition of cystine in the tubules and the interstitial tissue of the kidney could well explain why the kidney function in Lignac Fanconi's syndrome becomes progressively worse. Ultimately, this cystinosis of the kidney will lead to progressive tubular malfunction and glomerular fibrosis.[13]

Recently, a small group of adult patients have been reported who suffer from the adult form of Lignac Fanconi's disease.[22,24a] In these adult patients the cystinosis is very much in the background,[26] but marked hypophosphatemia, hyperphosphaturia, renal glycosuria and ammoaciduria without ammoacidemia are all present. The added signs of a defective function of the distal convoluted tubule, i.e., alkaline urine and mild systemic acidosis, are still more marked than in the infantile form. Due to the involvement of the lower part of the nephron, the hypercalciuria in the adult patients with Lignac-Fanconi's disease is much more intense (p 48) than in the infantile form. In 2 of the 18 adult cases described, both the Lignac Fanconi syndrome and multiple myeloma were present. [11,26] This coincidence may well be explained by damage to the tubular apparatus under influence of the reabsorbed Bence Jones and other abnormal proteins.

HYPERCHLOREMIC TUBULAR ACIDOSIS

Hyperchloremic tubular acidosis, or Butler Albright's syndrome (Lightwood Albright's anacidogenesis) is found in adults, infants and young children.[16] In the latter age group the disease frequently takes a fatal course. In

this syndrome the impairment of the function of the distal tubule is the outstanding manifestation, whereas the disturbance of the proximal tubular function is absent or minimal. The defective function of the distal convoluted tubule may be due to a congenital anomaly, however, chronic pyelonephritis and administration of large doses of sulfanilamide are also possible causes. The latter compound is toxic to the carbonic anhydrase system of the kidney and therefore impairs the bicarbonate reabsorption.

This condition can be diagnosed when an alkaline or slightly acid urine is secreted in the presence of hyperchloremia and a low bicarbonate level of the serum, as manifested by a reduced CO_2-combining power of the serum (p 43). Urinary ammonia is absent or diminished. Hypercalciuria and hyperpotassuria lead to hypocalcemia and hypopotassemia. Since a close association often exists between hyperchloremic tubular acidosis and Lignac Fanconi's syndrome,[20] hyperphosphaturia and hypophosphatemia are common. At the same time, polydipsia and polyuria are present. It must be added that moderate glomerular dysfunction is also usually found.

Often the hyperpotassuria is especially marked in this syndrome. Potassium ions compete with hydrogen ions in the tubular cells for excretion into the tubular lumen, in exchange against sodium ions present in the lumen of the tubules.[8] Since in tubular acidosis no hydrogen ions are formed in the tubules, the potassium elimination becomes unbridled and hypopotassemia is usually more severe than hyponatremia, or even hypocalcemia.

In hyperchloremic tubular acidosis, nephrolithiasis and nephrocalcinosis (PLATE 6a) frequently occur probably due to the combination of the marked hypercalciuria and the alkalinity of the urine. The calcium precipitation takes place in the pyramids, as a result of the concentration of calcium and alkali during the passage of the urine through the distal convoluted and the collecting tubules. Among the symptoms and signs caused by this tubular disturbance, weakness due to the loss of large amounts of potassium in the urine and ensuing hypokalemia may be prevalent. In this condition, vitamin D-resistant rickets or osteomalacia develop under influence of the excretion of excessive amounts of phosphate and calcium. Here, too, the symptoms and signs are similar to the skeletal disease which develops under influence of avitaminosis D

Large doses of a mixture of citric acid and sodium citrate considerably reduce the hypercalciuria—and, therefore, the rickets and osteomalacia. This mixture was originally advocated by Shohl for the treatment of experimental rickets due to acidosis and phosphate retention. Daily doses of 120 cc. of a solution containing 16 grams of citric acid and 12 grams of sodium citrate are recommended. This regimen has a favorable effect in tubular acidosis, because the slight acidosis in the upper part of the intestine caused by the citric acid of the mixture allegedly favors the absorption of calcium. However many authors doubt the validity of this statement. Be this as it may, the sodium citrate of the mixture decidedly improves the acidosis, for the citrate is burned in the body and the sodium is added to the depleted pool of fixed base. The elevation of the blood bicarbonate level helps to reduce the amounts of acid excreted in the urine. This decreases the amounts of basic radicals (and calcium) lost in the urine, making more calcium available for ossification. The additional administration of a few grams of calcium gluconate is helpful. Administration of basic sodium phosphate has also been recommended.[5]

In one of our patients[17] with tubular acidosis, treatment with Shohl's mixture raised the CO_2-combining power of the plasma from a level of approximately 30 volumes per cent to 45 volumes per cent. At the same time, the serum chlorides were lowered from 680 milligrams per cent to 610 milligrams per cent. The daily urinary excretion of calcium on a Bauer Aub diet decreased from approximately 400 milligrams to 150 milli-

grams. The osteomalacic changes of the bone readily changed for the better During this period the patient rapidly gained weight and became stronger, so that after a few months he was able to resume his normal activities. The underlying anomaly of the renal function, however, was not improved, when the citric acid sodium citrate was withheld for a short period, hyperchloremia and acidosis reappeared.

After the treatment with Shohl's mixture had been maintained for a long time, this patient started to complain about extreme fatigue. This was proven to be caused by hypokalemia, which was easily corrected by the administration of potassium chloride.

Saville et al. also emphasize the dangers of hypokalemia in this condition, which is often intensified under influence of sodium salt administration.[19] In order to avoid this complication they give tablets containing one part potassium bicarbonate and three parts sodium bicarbonate, with highly satisfactory results. Other authors give 30 cc. of a mixture of 140 grams of citric acid five times daily, 75 grams of sodium citrate and 25 grams of potassium citrate, dissolved in 1 liter of water.[21] In this way, both acidosis and hypokalemia are corrected simultaneously and remarkable improvement can be obtained.

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Chapter 5

Hypervitaminosis D

In humans huge doses of vitamin D must be administered before signs of toxicity develop. It is generally accepted that in adults, a daily dose of 20 000 I U of vitamin D per kilogram body weight is necessary before the syndrome of hypervitaminosis D results. These dangers were practically nonexistent as long as products containing natural vitamin D, such as non-fortified cod liver oil, were used. However, tremendous doses can easily be given in the form of irradiated ergosterol or calciferol. In later years, children with vitamin D–resistant rickets, patients with rheumatoid arthritis, and, in Europe, patients with lupus vulgaris, have been treated over a period of several weeks or months, sometimes even years[11] with daily doses of calciferol, equivalent to 500,000 I U of vitamin D Recently milk powder fortified with large amounts of vitamin D has proved to be toxic to infants (p. 52) Under such conditions, serious symptoms and signs may develop.[6,7]

As mentioned previously vitamin D not only causes increased absorption of calcium from the intestine, but also influences phosphaturia and, finally it modifies the enzymatic processes, which are responsible for enchondral and endosteal ossification. Remarkably enough, massive doses of vitamin D increase bone resorption more than calcium accretion.[1] The moderate daily doses of 3000 to 5000 units of vitamin D given in rickets and osteomalacia are sufficient to improve the impaired absorption of calcium from the intestine. The resulting increased calcium accretion of the rachitic bone far exceeds the discrete increase of the resorption of bone that results from these moderate doses of vitamin D

When larger doses of vitamin D are given, a point must be reached where complete absorption of all calcium present in the intestinal lumen takes place. When still more vitamin D is given, bone resorption augments accordingly, and, since no more calcium can be absorbed from the gut, resorption of bone must ultimately result. Thus, hypercalcemia, hyperphosphatemia, and hypercalciuria are all common signs of hypervitaminosis D The alkaline phosphatase of the serum remains normal.[4] In addition, marked and generalized resorption of bone (Plate 5*c*), together with metastatic calcification (Plate 4*b*) develop In cases where the hypercalcemia exceeds 17 mg per cent, the well known hypercalcemia syndrome develops, and anorexia, nausea, vomiting, constipation, excessive thirst, polyuria, apathy azotemia, and uremia may ensue.

The formation of calcium metastases is of special importance. These calcium deposits are formed in kidneys, blood vessel walls, heart, gastric mucosa, lungs, sclerae, falx, dura mater thyroid, pancreas, and periarticular soft tissues. Band keratitis due to calcium precipitation in the cornea must be specially mentioned. Calcium deposition in the media of the larger arteries occurs in the early stages of hypervitaminosis D This is especially true for the aorta, where calcium deposits are present between the elastic fibers. Only in far progressed cases is the intima involved.

The metastatic calcification in the kidneys is localized in the walls of the renal tubules, the medullary pyramids, the interstitial tissue and the calyces. Moderate microscopic calcification of glomeruli is present but the cortex is free of gross calcium deposits. This process

can often be visualized on roentgenograms in the form of nephrocalcinosis, limited to the medullary pyramids and the renal pelvis (PLATE 6a) In some cases, the calcium deposits in the kidneys remain microscopic in size and do not show up on the x rays. The albuminuria and the impairment of the kidney function may be just as serious here as when grossly visible nephrocalcinosis is present. Ultimately the metastatic calcification of the kidneys always leads to uremia. Renal stone formation has also been observed.

Bellman and Engfeldt have studied the kidneys in experimental hypervitaminosis D with microradiographic and microangiographic methods.[8] They mention that the changes of the glomeruli resemble the lesions found in human intercapillary glomerulosclerosis. The microangiograms reveal spasms in the efferent arterioles. Calcium deposition was found in all kidney structures and also in the Bowman's membrane of a small number of glomeruli. In hypervitaminotic rabbits, the roentgen micrograms show rather dense calcifications in the inner zone of the cortex. In the outer part of the cortex, just as in humans, only few and small calcifications are found.

In patients with rheumatoid affections who receive excessive doses of vitamin D the metastatic calcification is prevalent in para articular structures which have been damaged previously by arthritis, especially in bursae, synovial cavities and tendon sheaths.[8] This para articular localization of calcium deposits results in redness and swelling of the joints, which may give the impression of an acute rheumatoid arthritis. This, of course, is especially confusing in patients who are suffering from rheumatoid arthritis. The true nature of the pseudoacute arthritis, due to hypervitaminosis D can easily be recognized by x ray examination as being due to para articular calcification. It must be added that in rheumatoid arthritis, as in other diseases, hypervitaminosis D also causes calcium deposits in other organs. This is evidenced by the development of nephrocalcinosis and uremia in such patients.

It is of the greatest importance to recognize hypervitaminosis D as the cause of uremia, because after cessation of the vitamin D intake, calcium and phosphorus both of serum and urine go down to normal levels and the renal function improves. The abnormal calcium deposits in the para-articular structures are slowly resorbed (PLATE 4c) The resorption of small calcium deposits near the interphalangeal joints may take one year. Larger para articular deposits remain unchanged for a much longer period.[11] The generalized bone resorption also disappears very slowly, but ultimately recalcification can be demonstrated on the x-rays.

For the differential diagnosis, other conditions must be considered in which generalized bone resorption, hypercalcemia, hypercalciuria, and metastatic calcification are found at the same time. Fortunately this combination does not occur too frequently First, hypervitaminosis D needs to be differentiated from hyperparathyroidism. Hypophosphatemia often occurs in the latter condition in hypervitaminosis D the serum phosphorus is usually slightly increased. In renal osteodystrophy the serum calcium is nearly always low or at best normal, and urinary calcium and phosphorus excretion are decreased. In long standing alkali ingestion as in ulcer patients, only hypercalcemia exists—there is no hypercalciuria. The reverse is true in hyperthyroidism the serum calcium is normal, the urinary calcium is increased. In sarcoidosis, the skin and visceral manifestations usually permit a differentiation of this disease from hypervitaminosis D.

Since the dangers of the administration of excessive doses of vitamin D are common knowledge, hypervitaminosis D in adults has become a rarity However in infants, at least in the United Kingdom, a new syndrome, "idiopathic hypercalcemia," which may well be a result of hypervitaminosis D has now been recognized. A recent report mentions that between 1953 and 1955, 204 such patients have been observed, mainly infants between 4 and 8 months of age.[8]

In the malignant form of this disease

dwarfism, mental retardation, microcephaly and cerebral signs are present. The benign form is reversible and is of considerable clinical importance. Children with benign idiopathic hypercalcemia usually suffer from loss of appetite, tenacious vomiting and constipation. A systolic murmur can often be heard either at the point of maximal impulse or all over the precordium. Hypercalcemia and hypercalciuria are constant findings, the serum phosphorus and alkaline phosphatase remain usually normal, and blood urea, nitrogen and cholesterol are increased.[8,9] Under adequate treatment these abnormal values rapidly return to normal and the systolic murmur disappears.

Nephrocalcinosis has been frequently observed. Linear deposition of abnormally dense bone near the epiphyses of the long bone and osteosclerosis of skull base and vertebral bodies may be present.

There is strong evidence that hypervitaminosis D may play an important role in the etiology of this syndrome. "National Dried Milk," a popular food for infants in the United Kingdom, contains "not less than" 1200 I.U. of vitamin D per reconstituted liter, probably more. The vitamin D content of several other milk preparations used for infant feeding in England is even higher. The "British National Cod Liver Oil Compound" contains not less than 700 to 800 I.U. of vitamin D per teaspoonful, probably more. Cereals are also fortified, some brands containing 1500 I.U. per ounce. Infants who receive 1.5 pints of reconstituted dried milk, 1 ounce of fortified cereal and one teaspoon of fortified cod liver oil may easily ingest about 4000 I.U. of vitamin D per day. This intake is far in excess of the 400 to 700 I.U. which, around 1940, were recommended as the daily intake for infants. The daily maximal intake of vitamin D for infants was usually considered to vary around 1500 I.U.

In this connection it is of interest that in the United States no case of idiopathic hypercalcemia has been reported yet. In our country the most popular brand of evaporated milk contains only 420 I.U. of vitamin D per reconstituted liter. However, the possibility exists that cases of hypervitaminosis D in infants and children also may develop in the United States, since certain halibut liver preparations used in this country contain 6000 I.U. of vitamin D per teaspoonful.

Breast feeding has not yet become obsolete in England and it is interesting that until now no case of idiopathic hypercalcemia in breast fed infants has been reported. The vitamin content of human milk varies between 5 and 100 I.U. of vitamin D per liter, i.e., only 25 per cent of the vitamin D content of cow's milk.

In most cases of idiopathic hypercalcemia, feeding with low calcium milk powder (Locasol) and low calcium cereal (Glaxo), boiled in distilled water brought rapid recovery.[10] In other cases cortisone has been very helpful, mainly by inhibiting calcium and phosphorus absorption from the intestine.[9]

The British Pediatric Society has now decided to recommend that no foods fortified with vitamin D should be given to infants at all. Every infant, however, should receive cod liver oil of known potency.[3] This is exactly the same nutritional formula which was customary half a century ago.

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Chapter 6

Hypervitaminosis A

HYPERVITAMINOSIS A WAS FIRST ENcountered by Arctic explorers, who observed toxic effects resulting from the consumption of large amounts of livers of polar bears and bearded seals. Vomiting, exhaustion and peeling of the skin are known to occur after the eating of such livers. A meal of polar bear liver is also dangerous for dogs. It has gradually been recognized that this syndrome stems from acute vitamin A poisoning This is understandable if we consider that the livers of these animals contain 16 million units of vitamin A per kilogram.

Mellanby has demonstrated experimentally that vitamin A is an important controlling factor in the growth of bone. He found that the vitamin A concentration in the tissues necessary for the proper development of bone must remain within fairly narrow limits. In rats, for instance, avitaminosis A leads to an arrest of enchondral ossification. Confirming these results, Wolbach et al.[7,8] found that the administration of very large doses of vitamin A to rats changes the remodeling of the bones which takes place during the development of the skeleton. This in turn leads to characteristic changes of the shape of the long bones, especially the femur the tibia and the fibula. The epiphyseal disks are narrower than normal, the cortex of the diaphysis is reduced in diameter and an excess of osteoid tissue develops at the endosteal side of the shaft. In dogs, chicks and ducks[10] comparable results have been obtained.

Chronic hypervitaminosis A, which has repeatedly been observed in children, causes *completely different bone lesions.* Hyperostosis, the typical skeletal anomaly in hypervitaminosis A in children has never been observed in animals fed excessive doses of vitamin A.

After the first case of hypervitaminosis A in a child had been described by Josephs in 1944,[6] it soon became evident that this disease occurs only in children who are more than one year old. Probably a protracted latent period must elapse between the start of the excessive dosage and the appearance of clinical symptoms and signs. The possibility that the intestinal absorption of vitamin A is impaired during early life must also be considered. Actually most of the cases of hypervitaminosis A occur in two and three year old children.

Hypervitaminosis A as observed in the practice of medicine is usually caused by overdosage of oleum percomorphum, Navitol, or allied preparations. The children first become irritable, then complain of loss of appetite, insomnia and pruritus.[5,6,11] An erythematous rash develops, often the hair becomes coarse and sparse. Swelling and tenderness of the skeleton appear followed by limitation of motion. The deep swellings are firmly attached to the underlying bones. These lesions are especially frequent in the ulna (PLATE 7*c*) and the metatarsals (PLATE 7*b*) However the other bones of the arms and of the lower extremities may also be involved. Difficulties in gait occur frequently Hepatomegaly has repeatedly been found.

In the roentgenograms, the shafts of the bones appear to be thickened due to the deposition of large masses of bone upon the outer surface of the diaphysis. The shell like appearance of the hyperostosis is characterized by a zone of diminished density between the subperiosteal bone and the original cortex. Calcium and phosphorus of the serum are

normal, while the alkaline phosphatase is hardly ever increased.

The vitamin A content of the serum is very high and is increased from the normal levels of 50 to 150 I.U per cent to 400 to 2000 I U per cent. The diagnosis should only be considered if administration of large amounts of vitamin A can be proven. All subjective and objective signs disappear after cessation of the administration of vitamin A. Tenderness, hyperirritability and anorexia vanish within one week, but the bony manifestations of hyperostosis remain unchanged for several weeks or even months. Ultimately these lesions also gradually become less apparent. Such favorable reaction makes the diagnosis of hypervitaminosis A certain.

For differential diagnosis, infantile cortical hyperostosis, as described by Caffey should be considered (p 57) It can be mentioned here that children with Caffey's disease are always younger than six months and that involvement of the mandible is a prerequisite for the latter diagnosis.[2]

Until now five cases of hypervitaminosis A in adults have been described.[4] No bone lesions have been reported. Insomnia, loss of hair of scalp, eyebrows, eyelashes, axillary and pubic areas developed. Anorexia, loss of weight, and in some cases exophthalmos have been observed. All five cases complained of bone and joint pains and bone tenderness. Ossifying periostitis was found in only one patient, both at x-ray examination[3] and in a biopsy In the other four patients no bone lesions could be discovered. All symptoms and signs disappeared after cessation of the vitamin A administration.

Avitaminosis A causes hyperkeratosis of the skin, metaplasia of the epithelium of different organs, night blindness, changes of the conjunctiva in the form of Bitot's spots and, ultimately xerophthalmia. However, changes of the skeleton of humans have not been described in avitaminosis A, although in animals such lesions have been stud[illegible] extensively by Mellanby Wollbach, [illegible] others.[1]

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Chapter 7

Infantile Cortical Hyperostosis

THIS SYNDROME, DESCRIBED BY CAFFEY,[3] always develops within the first six months of life and is characterized by irregular new bone formation of flat and long bones. Infantile cortical hyperostosis occurs in both white and colored babies.[6] In the later stages of the disease, pudgy, doughy swelling of the soft tissues overlying the affected bones is nearly always present.[1] The soft tissue swelling over the jaw is often brawny in character General irritation and tenderness are late signs and indicate the presence of massive hyperostosis. Fever and leukocytosis are constant signs, at least during the acute phase of the disease. The cortical hyperostosis can involve any bone in the body but the jaw (PLATE 6*e*) the clavicles (PLATE 6*b*) and the ribs are always affected. Roentgenologically, the marked cortical apposition of bone is highly significant.[7] The newly formed bone may even become irregular and sclerotic.[4] The cortical hyperostosis always involves the entire length of the bone[8] (PLATES 6 *b c d*) Sometimes marked distortion of the facial features results from the hyperostosis of mandible or maxilla. The soft tissue swelling over the affected bone may develop before or after roentgenologic bone lesions can be visualized.[8] In general, it can be stated that in the early stages only roentgenologic signs can be elicited. No etiologic factor has been recognized which could cause this condition. However cases are known where several siblings suffered from cortical hyperostosis, thus presenting the possibility that hereditary factors could play a role.

The disease is self limited. Under patient observation the signs and symptoms gradually clear up, the hyperostosis disappears and no sequelae are left behind. No treatment is known which could hasten this favorable development.

For differential diagnostic purposes, hypervitaminosis A above all must be considered. The bone lesions and the tender soft tissue swelling are the same in both diseases. In Caffey's disease, however, hyperostosis of the mandible is always present, usually leading to swelling of the face. As far as is known, this localization has never been seen in hypervitaminosis A. The frequent metatarsal lesions of the latter ailment are very rarely observed in Caffey's disease.[3] The entire length of the bone is involved by the cortical hyperostosis, while in hypervitaminosis A only part of the bone is thickened. In addition, children with Caffey's disease are usually younger than six months and nearly always present fever leukocytosis and a high sedimentation rate. Finally, in these children there is no history of excessive vitamin A intake, and the vitamin A content of the serum is not high. Even if by coincidence moderate amounts of vitamin A have been ingested in a case of Caffey's disease, the bone lesions persist after cessation of vitamin A administration.

The differential diagnosis should perhaps also consider bone lesions due to syphilis or scurvy, or even rickets. Serologic reactions for syphilis, hemorrhagic tendency and changes in ossification center and metaphysis in scurvy (p 26) and the abnormalities of the epiphyseal plates in rickets (p 39), will easily exclude these three possibilities.

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Chapter 8

Hyperparathyroidism

OUR KNOWLEDGE OF HYPERPARATHYroidism, or diseases due to hyperfunction of the parathyroids, began in 1891 when von Recklinghausen[83] described a new disease which he named generalized fibrocystic osteitis with multiple "osteosarcomas." These so-called osteosarcomas today are more correctly designated as giant cell tumors or osteoclastomas (p 69)

Twelve years after Recklinghausen's original description, Askanazy[4] published the results of an autopsy performed on a case of "osteitis deformans without hyperostosis." In this patient generalized "decalcification" of the skeleton and a tumor of one parathyroid —a "parastruma"—were found. It has since been recognized that this patient actually suffered from Recklinghausen's bone disease. Askanazy commented that "in the future, relations between tumors of the thyroid gland or other endocrine organs and decalcifying affections of the skeleton may well have to be considered." The perspicacity of this remark has been proven by the course of events. After 1910 the number of observations in which a parathyroid adenoma was discovered at the autopsy of patients with lesions of the skeleton gradually increased. As early as 1915 Schlagenhaufer suggested that an attempt be made to extirpate the parathyroid adenoma in such patients.[88] Following this suggestion, in 1925 Mandl explored the thyroid region of a patient with Recklinghausen's bone disease and removed a parathyroid adenoma. He obtained a remarkable improvement of the skeletal disease —an improvement which lasted for more than five years.[43,44] Mandl observed, on repeated urinalyses, that the excessive preoperative urine calcium excretion was reduced to normal levels immediately following the removal of the adenoma.

At the end of 1928 Gold, also in Vienna, reported the second favorable result of a parathyroidectomy in this disease. In February, 1929, when only Mandl's report was known to us, a parathyroid adenoma was successfully removed in one of our patients.[40] In the same year this operation was performed in several other countries. Between 1926 and 1945 reports of 295 operative cases had been published.[40] During the same period 42 parathyroid adenomas had been discovered at autopsy[40] In 1953 Black[10] reviewed 112 cases operated on in the Mayo Clinic, where today between 15 and 20 cases are diagnosed each year More than 600 such cases have now been reported in the literature. The results of the clinical studies in this field, which were sparked by Mandl's original publication, have elucidated many problems of the pathology of skeletal diseases. In addition, our knowledge of calcium and phosphorus metabolism has increased, light has been shed upon the pathogenesis and treatment of certain forms of nephrolithiasis, and the etiology of individual cases of renal failure has been explained. Other divisions of medicine have profited by it as well.

An introduction to the anatomy of the parathyroids is necessary before we discuss the clinical aspects of the different syndromes caused by hyperparathyroidism.

ANATOMY

The parathyroids are the smallest endocrine glands in the body In man, the two superior parathyroids were described in 1880 by Sandström, while in 1895 Kohn described

the two inferior parathyroids. As a rule, the parathyroid glands are situated on the posterior surface of the thyroid. In 80 per cent of the cases examined, four parathyroids were found, in 14 per cent, less than four and in 6 per cent, more than four.

In several cases in which only two or three parathyroids were found, their relatively small weight suggested that not all the glands had been discovered. On the other hand, an autopsy of a patient with nine hyperplastic glands has been reported by Rogers.[63]

The parathyroids vary between 6 and 8 millimeters and 3 and 4 millimeters in width. Other authors mention variations in length between 4 and 15 millimeters. Averaged from the figures of different authors, the weight of each separate parathyroid ranges between 0 038 and 0.047 grams. The total weight of the four parathyroids together varies around 0 170 grams. Some authors claim 0 140 grams as the total weight of the four parathyroids.

Considerable variations in size and weight of the normal parathyroid glands have been recorded. In three exceptional cases a total weight of 306 314 and 388 milligrams, instead of the average of 170 milligrams for the four parathyroids, has been registered.[64] In view of such variations, the small size of many of the parathyroid adenomas removed in the Mayo Clinic deserves special men-

In man, the parathyroids are prac always situated outside the capsule of thyroid gland. However, as a rarity on more parathyroids may be found, appare embedded within the substance of the thyr gland. In such cases the parathyroids a located in a deep fissure of the thyroid glan which, in turn, is covered by a fold of the thyroid capsule. When a parathyroid gland is found in such a fissure, the small gland is still situated on the outer aspect of the capsule.

EMBRYOLOGY

Under normal conditions, the superior parathyroids are located at the middle third of the posterior surface of the thyroid, the level where the inferior thyroid artery enters the gland. The inferior parathyroids are often found near the lower edge of the thyroid gland. The ontologic development of these glands explains why the parathyroids are so often discovered in aberrant positions. The superior parathyroids together with the thyroid gland are derived from the fourth branchial cleft, the inferior parathyroid glands together with the thymus from the third branchial cleft. During the development of the embryo the superior parathyroids migrate downward together with the thyroid and the inferior parathyroids with the thymus. In the course of this migration the inferior parathyroids must necessarily cross the superior glands. Aberrant inferior parathyroids, therefore, may be situated anywhere from the site of origin of the thymus to its final resting place in the anterior mediastinum (p. 63). Aberrant superior parathyroids may be found between the thyroid and esophagus, within the carotid sheath, behind the innominate vein, or even in the posterior mediastinum.

HISTOLOGY

Three different cells are present in the parathyroids (1) chief or principal cells (Welsh cells) (2) water-clear cells (Getzowa cells) and (3) eosinophilic cells. A cell intermediary between a principal cell and a water-clear cell has been designated a transitional chief cell or a young chief cell.[65] Infantile parathyroids consist only of young chief cells.

Many authors are of the opinion that the principal cells represent the resting phase, that the transitional chief cells are activated principal cells and that the water-clear appearance of cells indicates maximal functional

activity Eosinophilic cells are considered to have little or no endocrine function. As pointed out by Eger and associates, the glycogen content of the cells of the parathyroid glands parallels the intensity of the function.[21,22]

PHYSIOLOGY[7a]

The specific endocrine function of these tiny glands became evident when the rapid drop of the serum calcium caused by the removal of the parathyroids was described in 1908 At the same time it was recognized that tetanic cramps appeared every time the serum calcium fell below a certain value.

An active parathyroid preparation was obtained in 1925 by Collip Originally named parathormone, the agent is now called parathyroid extract. The designation parathormone was abandoned because the extract is prepared by the extraction of the glands with 10 per cent hydrochloric acid in a boiling water bath. It seems hardly possible that after this procedure unchanged parathyroid hormone could still be present. The activity of the extract is standardized by its influence upon the serum calcium of experimental animals. Recent investigations of Davies and Gordon[19,20] indicate that standardization of the parathyroid extract might be improved if the influence of the preparation upon the phosphorus content of serum and urine was also bio-assayed. Administration of parathyroid extract by mouth has no influence upon the calcium metabolism. It must be added that peroral administration of either A.T 10 or Vitamin D often leads to the same salutory results in hypoparathyroid tetany as the subcutaneous injection of parathormone.

Gradually it is becoming evident that parathyroid hormone has a dual influence upon the condition of the skeleton. This hormone stimulates the function of the osteoclasts and, in addition, increases the excretion of phosphate by direct action upon the kidney function. The hyperplasia and hyperfunction of osteoclasts caused by the hormone leads to rapid osteoclastic erosion of bone, resulting in fibrous osteitis. This direct influence of parathyroid extract upon bone has been demonstrated by the ingenious experiment of Barnicott, who transplanted a splinter of bone, along with parathyroid tissue, into the brain of a mouse.[6] After two weeks, osteoclastic bone resorption was apparent at the site of the bone which had been adjacent to the transplanted parathyroid. Hwei-Ya Chang obtained comparable results by grafting parathyroid tissue below the external periosteum of the parietal bone of young mice or rats.[15]

Gaillard confirmed these observations by cultivating in vitro the parietal bone of mouse albino embryos, together with parathyroids of the same embryo.[27] The parathyroid tissue was placed in direct contact with the inner periosteum of the bone. Proliferation of large multinuclear osteoclasts developed and absorption of the bone explants resulted. In tissue cultures where bone fragments were brought into contact with a slice of human parathyroid adenoma, the same results were obtained. It must be added that often some absorption of bone could be seen after four days—at a time when no osteoclasts had yet developed.

Microroentgenography reveals numerous large resorption cavities with irregular boundaries in the bone tissue of animals injected with parathyroid extract. At the same time, many newly formed osteons can be recognized by their low mineral content. Radioautographic images of bone sections of young animals treated with parathyroid hormone and injected with radioactive phosphorus reveal that incorporation of phosphorus is delayed by the injection of parathyroid hormone.[34] This result seems to indicate that in young animals, at least, destruction of bone under influence of parathyroid extract exceeds the regeneration.

It is now generally believed that the increased osteoclastic activity, which takes

place under influence of parathyroid hormone, primarily attacks bone matrix, resulting in liberation of calcium phosphate. As a matter of fact, before actual resorption of bone takes place under influence of parathyroid extract, changes of the bone matrix can be observed in the form of depolymerization of the polysaccharides. Moreover injections of parathyroid extract cause an increase in the mucopolysaccharides circulating in the blood. These findings indicate that under the influence of parathyroid extract destruction of mucopolysaccharides of the bone matrix, especially chondroitin sulfuric acid takes place.

Albright and his associates first demonstrated that parathyroid extract has a remarkable influence upon phosphorus metabolism that is completely independent of the osteoclastic absorption of bone.[3] They observed that the injection of parathyroid hormone in humans causes a considerable increase in the amounts of phosphates excreted in the urine. This has been confirmed by Brull[13] in the following elegant experiment. A dog's kidney was grafted to the large vessels in the neck of the same dog. When this explanted kidney was perfused with the blood of a dog which had received an injection of parathyroid hormone, much more phosphate was excreted than when the blood of a normal dog was used for the perfusion. Harrison and Harrison have demonstrated that the hyperphosphaturia caused by parathyroid hormone is due to a decrease in the reabsorption of phosphates by the renal tubules.[21] Although many physiologists have disagreed with the Harrisons, recent publications strongly support their conclusions.[22]

Shortly after the hyperphosphaturia under influence of parathyroid hormone has started, the amount of calcium eliminated with the urine also increases. This hypercalciuria is probably due to the increased glomerular filtration caused by parathyroid hormone, rather than to inhibition of the reabsorption of calcium by the renal tubules.

It is now generally accepted that the changes of calcium and phosphorus metabolism in the intact animal following injection of excessive amounts of parathyroid extract are due to the combined result of the action of this hormone on the skeleton and on the phosphorus excretion by the kidney.[8] The enhanced osteoclastic bone resorption that takes place under influence of parathyroid extract must cause the liberation of calcium and phosphate. Under these circumstances, both calcium and phosphorus in serum and urine might be expected to increase. However, as soon as the parathyroid extract leads to erosion of bone and to liberation of calcium phosphate, the excess of liberated phosphate is excreted in the urine. This leads to hypophosphatemia, whereas hypercalcemia and hypercalciuria persist.

Thus, in patients with hyperfunction of the parathyroids—so-called hyperparathyroidism—the following biochemical syndrome nearly always is present

(1) Hypercalcemia

(2) Hypercalciuria

(3) Hypophosphatemia

(4) Hyperphosphaturia

Without the presence of this biochemical syndrome, the diagnosis of hyperparathyroidism is doubtful. In the light of this dual action of parathyroid hormone, many authors have discussed the possibility that parathyroid extract may contain two hormones, one influencing calcium metabolism, the other phosphorus metabolism.[11] Final proof for this contention has not yet been obtained.

The osteoclastic bone resorption leads to secondary bone repair. When the latter develops, the activity of the osteoblasts causes an increase in the alkaline phosphatase of the serum. It follows that in hyperparathyroidism, an increase of the alkaline phosphatase can always be expected when clear-cut bone changes can be discovered by roentgenologic examination. There are so few exceptions to this rule that in a patient

with widespread bone resorption, the absence of an increased alkaline phosphatase content of the serum is a strong point against the diagnosis of hyperparathyroidism. Contrariwise, in cases of hyperparathyroidism with limited roentgen changes of the skeleton, the alkaline phosphatase of the serum is not increased.

As far as is known today, the function of the parathyroids is not regulated by any hormone secreted by the anterior lobe of the pituitary

ETIOLOGY

Hyperparathyroidism is commonly caused by adenoma formation in one or more parathyroid glands, or rarely, by a primary hyperplasia of all four parathyroids. In exceptional instances it is caused by a carcinoma of one of the parathyroids. The quantitative relationship existing between these three possibilities is elucidated by the following figures Since 1925 around 600 cases of hyperparathyroidism caused by adenoma formation have been published, as opposed to about 40 cases due to primary hyperplasia[10,32] and about 15 or 20 cases due to parathyroid carcinoma.[50]

Whereas in the majority of hyperparathyroidism cases only *one* parathyroid adenoma is present, multiple adenomas have been found in many instances. Norris[40] reports 20 instances of multiple adenomas among 322 cases of hyperparathyroidism. Black found 10 among 112 cases.[50] In two of Black's 10 cases three adenomas (in one case even four adenomas) were found. We also recently saw two patients with hyperparathyroidism, each with four adenomas. In addition, we received information that five adenomas had been encountered in another patient. Hellström had only one patient with two adenomas among 50 cases of hyperparathyroidism.[32]

The adenoma formation occurs about four times more frequently in one of the lower parathyroid glands than in one of the superior ones. Since, as mentioned above, the parathyroids are often aberrant, the operation for a parathyroid adenoma frequently requires a careful exploration of many planes of the neck and also of the anterior mediastinum. In exceptional cases even this may not be sufficient. In one of our patients the parathyroid adenoma was located in the posterior mediastinum to the right side of the esophagus opposite the seventh rib

Among 281 cases collected by Norris, 30 aberrant adenomas were present.[40] In 19 of these 30 the adenoma was located in the mediastinum in 9 within the substance of the thyroid gland and in 2 behind the esophagus. The finding of an aberrant adenoma is usually difficult unless a separate vascular pedicle, which starts from the inferior thyroid artery and leads to the displaced adenoma, can be recognized.[40]

Parathyroid adenomas consist either of proliferating chief cells or of proliferating transitional chief cells, i.e. small water-clear cells. Since the oxyphilic cells have little or no endocrine function, a true oxyphilic adenoma can hardly be the cause of hyperparathyroidism. A few hyperfunctioning adenomas consisting wholly of oxyphilic cells have been reported. In these adenomas actually oxyphilic clear cells or oxyphilic transitional cells were present.[40,50]

The weight of the adenomas, studied by Norris,[40] varied considerably, the smallest tumor recorded weighing 0 4 gram, the largest, 120 grams. The smallest tumor Hellström[32] observed measured 1 centimeter In contrast, the Mayo Clinic[10] reports that 3 per cent of the adenomas removed weighed less than 100 milligrams 22 per cent, less than 500 milligrams 34 per cent, less than 1 gram. The preponderance of these very small tumors in the Mayo Clinic series may be explained by earlier recognition in this more recent survey It is true that in general, the average size of the adenomas is larger in more advanced cases with extensive bone lesions. However, exceptions to this rule

occur Surprisingly the second smallest case in the Mayo Clinic series, weighing 54 milligrams, was found in a patient with typical, generalized fibrous osteitis.

For the differentiation of small adenomas from somewhat enlarged normal parathyroids the following criteria may be helpful. Parathyroid tumors have a brown color Inasmuch as fat is present in normal parathyroids and absent in adenomas, the latter are darker than the normal parathyroid glands. Still more important for this differentiation is the presence of a rim of normal parathyroid cells, surrounding a small adenoma. The latter finding is pathognomonic of the diagnosis of a parathyroid adenoma. Cystlike spaces and calcareous deposits are frequent findings in parathyroid adenomas and may well be due to previous hemorrhages. Cases of infarction of an adenoma have been described.[24]

Hyperplasia of all four parathyroids was first reported in the Dutch literature by Beyerinck,[23] who studied a patient with hypercalcemia, varying between 19.3 and 21 mg. per cent, and hypophosphatemia, varying between 2 and 2.5 mg per cent. Hypercalciuria was also present. At operation, Beyerinck found a coffeebean sized parathyroid tumor The patient died the next day At autopsy three more parathyroid tumors were found, the size of a hen's egg, a pigeon's egg and a coffeebean, respectively Subsequently re-examination of the histologic sections of the parathyroid tumors revealed that these consisted exclusively of large water-clear cells no other cells were seen.

Albright and co-workers[4] later also reported that in certain cases of hyperparathyroidism, a hyperplasia or hypertrophy of all four parathyroids may be present. Usually the four parathyroid glands are not equally enlarged often one or two of the glands are only moderately enlarged, whereas the other glands are markedly increased in size. This generalized hyperplasia is due to a proliferation of water-clear cells, which are considerably larger than the normal cells and are arranged concentrically The average diameter of the cells is about 30 microns. Their nuclei are located in the periphery of the cells. These cells have a certain morphologic similarity to the cells of clear cell carcinoma of the kidney In generalized parathyroid hyperplasia, no principal cells or oxyphilic cells are found in the glands, and the intercellular substance is remarkably scanty The total weight of the four hyperplastic parathyroids is as a rule astoundingly high, varying between 3 and 52 grams. The disease is rare and, as mentioned above, only about 40 cases have been reported (p 63)

It is now certain that the syndrome of hyperparathyroidism is fundamentally the same, whether it be caused by a parathyroid adenoma or by a generalized hyperplasia. However all cases of generalized hyperplasia with or without generalized osteitis fibrosa eventually develop renal stones. The generalized bone resorption, if present, is usually moderate.

Several cases have been described where multiple parathyroid adenomas were combined with an adenoma of the pituitary gland and with one or more islet cell adenomas.[44] A few instances of hyperparathyroidism in siblings have been reported.[39]

Hyperparathyroidism due to a malignant tumor of the parathyroids has repeatedly been observed. The manifestations of hyperparathyroidism, which may disappear after removal of the malignant parathyroid adenoma, all return when a *local* recurrence of the tumor or a metastasis to the regional lymph glands develop. Metastatic deposits *have also been observed in* lung, liver and kidney In 1948, Norris recognized only 15 cases of hyperparathyroidism due to parathyroid carcinoma, although at that time 41 such cases had been reported in the literature.[49] Since then several new cases have been published. O'Donovan,[50] who reported another proven case of hyperparathyroidism due to carcinoma of one parathyroid, is more conservative than Norris in his estimate of the incidence of functioning parathyroid car

cinomas. In his opinion not more than 13 proven cases can be found in the literature. Janelli accepts 23 such cases.[37]

Recently, another instance of carcinoma of the parathyroid causing the clinical picture of hyperparathyroidism has been observed in the Cook County Hospital. This is the same institution from which Meyer and his associates reported the first such case.[48] At admission, the patient was in the third trimester of pregnancy and gave an ill defined history of bone pains and weight loss. A routine x ray of the chest revealed osteolytic areas in the clavicles and in the head of the humerus. This prompted a biochemical study which elicited the classical syndrome of hyperparathyroidism. Because weight loss and anemia suggested the possibility of a neoplasm, an aspiration of the sternal marrow was performed This showed the presence of nests of tumor cells. It was then apparent that the patient presented signs of both hyperparathyroidism and an occult carcinoma. The primary site of the neoplasm could not be identified at that time. At necropsy, a carcinoma of the parathyroid gland was present, but no metastases could be found at gross examination

In general, it may be said that parathyroid carcinoma producing hyperparathyroidism is rare, but should be considered in all patients who present classical clinical signs of hyperparathyroidism and, at the same time, evidence of a malignancy It may well be that the parathyroid carcinoma has a tendency to metastasize to the bone marrow and that a sternal puncture would prove to be a valuable diagnostic tool in such cases.

BIOCHEMICAL FEATURES

In most laboratories the values found for the calcium content of normal human serum average around 10.4 mg per cent. In a recent publication, the mean of the normal values for serum calcium, however has been reported to be 9.2 ± 0.7 mg per cent.[22] In hyperparathyroidism, the serum calcium is practically always increased above 11 mg per cent, in 80 per cent of the cases above 12 mg per cent. It may even reach 23 mg per cent,[60] and 30 mg per cent. Cases of hyperparathyroidism with a normal calcium content of the serum (but not below 10 mg per cent) have always been considered to be rare, occurring mainly when the disease is complicated by severe renal insufficiency, by avitaminosis D and perhaps by hypoproteinemia.

Spontaneous remissions of hyperparathyroidism may occur in the course of the disease. Thus, hyperparathyroidism should not be excluded in a suspected patient when occasionally in the course of the disease, normocalcemia has been found. This is well illustrated by the interesting case of hyperparathyroidism with normal serum calcium discussed by Castleman.[15] It later was discovered that on three different previous occasions, a genuine hypercalcemia varying between 12 and 14 mg per cent had been found in this patient.

Repeated determinations of the serum calcium of 10 patients with proven hyperparathyroidism of Chambers et al.[10a] revealed in 9 patients values always above 11.8 mg per cent. On the other hand, in 5 of 10 proven cases of parathyroid adenoma recently admitted to the hospital of Duke Medical School, serum calcium values below 10 mg per cent were occasionally found. It must be added that none of these 5 patients had normocalcemic values at *all* times during the observation. In all these patients, hypercalcemia from time to time occurred—to wit, 11.0, 11.2 11.8, 13.9, and 15.4 mg per cent, respectively [21]

Cases of hyperparathyroidism with only a slight or moderate increase of serum calcium seem to occur more frequently today than 25 years ago. In this connection, it seems important that the clinical syndromes under which hyperparathyroidism presents itself are also changing This undoubtedly is the result of wider understanding of this disease and a

more extensive use of the determinations of serum calcium and phosporus. The disease is now usually recognized in its incipient stages before the patient has been reduced to skeletal invalidity

The decrease of the inorganic phosphorus of the blood below 3 mg per cent is diagnostically important in hyperparathyroidism because it occurs only rarely in other diseases. It is also observed in osteomalacia (p. 33) and in the different modalities of the Lignac Fanconi syndrome (p 43) but in both of these diseases hypocalcemia is usually present.

In every patient with serum phosphorus values below 3 mg per cent, together with high or even high normal values for serum calcium, the presence of hyperparathyroidism must be seriously considered. For instance, in a patient with proven Boeck's sarcoids, hypercalcemia cannot always be ascribed to the presence of sarcoidosis alone (p 102) If not only hypercalcemia, but also hypophosphatemia are found in such a patient, search for a parathyroid adenoma is indicated. Hyperparathyroidism should also be considered if hypophosphatemia is encountered in a patient with hypercalcemia allegedly due to Burnett's syndrome (p 94) or to hypervitaminosis D

Unfortunately the decrease of the serum phosphate in hyperparathyroidism is found less frequently than the increase of the serum calcium, and in a number of cases the serum phosporus is normal. Only in 4 of the 10 patients with hyperparathyroidism examined by Chambers et al. was the serum phosphorus always found to be below the lowest normal value observed by these authors, i.e. 2.4 mg per cent.[144] In addition, the impairment of the renal function that so frequently occurs in hyperparathyroidism causes an increase in the inorganic phosphorus of the serum. In the initial stages of the renal involvement, the hypophosphatemia of the patient with hyperparathyroidism changes to normal values in the later stages true hyperphosphatemia is found.

It should be repeated that an increase of the alkaline phosphatase of the serum is not a sign of hyperparathyroidism per se. Only when the skeletal signs of hyperparathyroidism develop—i.e. in Recklinghausen's bone disease—does the alkaline phosphatase rise to values exceeding 5 Bodansky units or 15 King Armstrong units per 100 cc. Such an increase of the alkaline phosphatase of the serum is far from pathognomonic of Recklinghausen's bone disease, because the same change is observed in all other bone diseases in which proliferation of osteoblasts occurs. The same holds true for obstructive jaundice and for all liver diseases in which an excessive proliferation of cholangioles or bile capillaries exists.

The amount of calcium eliminated in the urine in hyperparathyroidism is usually greater than normal. As long as hyperparathyroidism is not complicated by avitaminosis D or by a serious degree of renal insufficiency the calcium excretion in the urine follows the calcium in the serum. For a calcium balance in which both intake of calcium and the excretion of calcium in both urine and stools are determined, a well organized metabolic ward is necessary Such an experiment must extend over two or more periods of four days each. For practical purposes, the determination of the amount of calcium excreted in the urine on four consecutive days, on a low calcium diet, gives important diagnostic clues in cases of hyperparathyroidism. This test can easily be performed in an ordinary hospital ward. In normal people, 70 to 90 per cent of the calcium output appears in the stools, and only 10 to 30 per cent in the urine. In hyperparathyroidism, the greater part of the calcium is excreted in the urine.

For the demonstration of the hypercalciuria in hyperparathyroidism, we originally used a test diet containing 415 milligrams of calcium.[66, 61] With this diet, a normal person excretes 150 to 225 milligrams of calcium in the 24 hour urine and 1 to 2 grams of calcium in the stool collected for three

days. In cases of hyperparathyroidism, the daily excretion of calcium in the urine is usually much increased, often reaching 400 to 500 milligrams. The calcium-poor test diets of Bauer and Aub or of Albright and Reifenstein have become popular in this country.[2] On the Bauer Aub diet, which contains 2000 calories and 125 milligrams of calcium, the daily calciuria of normal individuals usually remains below 100 milligrams. When the calcium excretion exceeds 200 milligrams, the possibility of hyperparathyroidism must be seriously considered. Chambers et al. found that in 9 of 10 patients with proven hyperparathyroidism, the daily urinary calcium excretion exceeded 150 milligrams. In the rare cases of hyperparathyroidism in which no significant elevation of the calcium content of the serum is found, hypercalciuria may still persist. However there are no rules without exception—certainly not in medicine. There are, of course, many different conditions in which hypercalcemia and hypercalciuria can be found—e.g. multiple myeloma, hyperthyroidism, sarcoidosis, acute immobilization, hypervitaminosis D rapid spread of skeletal metastasis, Hodgkin s disease of the bones, nephrolithiasis, etc. In many of these diseases, x ray examination of the skeleton may reveal lesions which could be confused with the generalized fibrocystic osteitis of hyperparathyroidism. The ensuing differential diagnostic difficulties can perhaps be solved if the calcium content of the spinal fluid is determined The latter allegedly remains within the normal limits of 4.5 to 5.5 mg per cent in hyperparathyroidism, but increases in all other forms of hypercalcemia.[83]

In addition, cases of hyperparathyroidism with hypercalcemia but without hypercalciuria do occur Most authors agree that the hypercalciuria of hyperparathyroidism disappears when a severe degree of renal insufficiency develops. In such cases the kidneys are unable to eliminate the calcium. This may also occur however in cases of hyperparathyroidism in which a severe grade of avitaminosis D exists. In 1937, we reported a patient with hyperparathyroidism and hypocalciuria due to superimposed avitaminosis D.[81] Patients with chronic and painful bone disease are often obliged to stay indoors for many months. Without exposure to sunshine, no vitamin D is manufactured in the skin, furthermore, the appetite of such patients is also usually diminished and the oral intake of vitamin D is minimal. Under these circumstances, avitaminosis D—leading to hypocalciuria (p 37)—can easily develop We have also observed a case of hyperparathyroidism with moderate hypercalciuria, in which hypocalciuria developed during observation. This patient had been placed on repeated Bauer Aub test diets, containing only minimal amounts of vitamin D Thus, hyperparathyroidism with hypercalcemia but normal calciuria is less rare than was originally supposed. Such cases have also been observed in the Mayo and the Lahey Clinics. Hellström[82] recently reported that among his 50 patients with hyperparathyroidism, nine excreted less than 100 milligrams of calcium daily, ten excreted between 100 and 200 milligrams. In only eight of these patients was marked hypercalciuria found. It follows that hypercalciuria in hyperparathyroidism, though commonly observed is not a constant sign.

To avoid the quantitative determination of calcium in the urine, Barney and Sulkowitch devised a qualitative test. This method, when certain precautions are heeded, permits a rapid answer to the question whether the amount of calcium excreted in the urine is excessive. Their reagent consists of 2.5 grams of oxalic acid, 2.5 grams of ammonium oxalate, and 5 cc. of glacial acetic acid, dissolved in distilled water to a volume of 150 cc. This solution precipitates the calcium of the urine when the reaction is slightly acid. The reagent is mixed with equal amounts of urine. Under normal conditions, a slight to moderate precipitation of calcium occurs. If hypercalciuria exists, the precipitate is thick and milky Certain precautions are necessary

for the correct interpretation of this test. The Sulkowitch test should be done on a specimen of the total 24 hour urine, collected while the patient is on a calcium poor test diet. If these precautions are heeded, a strongly positive Sulkowitch test is a reason to suspect the possibility of hyperparathyroidism. This possibility must be confirmed by a careful quantitative analysis of the calcium metabolism. Consistently weakly positive Sulkowitch tests certainly militate against the presence of hypercalciuria.

The excretion of abnormal amounts of inorganic phosphorus is a characteristic sign of hyperparathyroidism. It is difficult to obtain a correct phosphorus clearance without strict supervision of the diet in a metabolic ward. On the other hand, in the presence of a serum phosphorus of 2.2 mg. per cent or lower a daily excretion of several hundred milligrams of phosphorus proves that the reabsorption of phosphorus in the renal tubules is impaired.

THE VARIOUS SYNDROMES OF HYPERPARATHYROIDISM

Patients with hyperparathyroidism and hypercalcemia often complain about lassitude and easy fatiguability. Polyuria, polydipsia, nocturia, palpitations, constipation, nausea, vomiting and occasionally dyspnea, occur. Bone pains, pathologic fractures, giant cell tumors, bone cysts, renal calculi, kidney infections, and ulcer signs all may be manifestations of hyperparathyroidism. Because of the protean manifestations of this disease, the following presenting syndromes have been designated:

1. *Recklinghausen's Bone Disease*
2. *Nephrolithiasis*
3. *Nephrocalcinosis*
4. *Hyperparathyroid Crisis or Acute Hyperparathyroidism*
5. *Digestive symptoms and signs*
6. *Diabetes insipidus-like syndrome and*
7. *Mental depression.*

RECKLINGHAUSEN'S BONE DISEASE

Von Recklinghausen,[44,45] in his two extensive monographs on diseases of the skeleton, described two patients with bone pains, softening of the skeleton and deformation due to pathologic fractures. Histologic examination revealed the presence of osteitis fibrosa generalized throughout the entire skeleton.

Recklinghausen was convinced that the osteitis fibrosa was specific for the disease he first described. It is now generally believed that any form of rapid bone destruction can lead to osteitis fibrosa. This histologic finding is therefore not limited to Recklinghausen's bone disease, but is also found in Paget's disease, chronic uremia, hyperthyroidism and sometimes even in rapidly progressive rickets. Nevertheless, there are certain histologic features which render a differential diagnosis between these different forms of osteitis fibrosa possible.

In Recklinghausen's disease, bone destruction is mainly the result of progressive osteoclastic bone resorption. The hyperactivity and accumulation of osteoclasts sometimes leads to the formation of giant cell tumors. The histologic picture reveals the presence of multiple Howship's lacunae and marked marrow fibrosis. New bone tissue is formed in this proliferating fibrous tissue, as indicated by the presence of osteoblasts. The thinned bone trabecules are often perforated by the proliferating fibrous tissue, the so-called dissecting bone resorption. The remnants of the bone trabecules are surrounded by osteoid seams which, as a rule are not so broad as in osteomalacia (p. 30). On the whole, the osteoclasia in the cortex and marrow is much more intense than the formation of new bone, thus ultimately leading to a generalized resorption of bone.

It must be added that experimental acidosis produced by administration of ammonium chloride can give rise to the same skeletal changes found in Recklinghausen's disease.

In addition to the generalized osteitis fi-

brosa, Recklinghausen also found cysts and brown tumors, the latter consisting of rapidly proliferating giant cells. These histologic findings led Recklinghausen to name this disease a generalized fibrocystic osteitis with multiple "osteosarcomas." These so-called osteosarcomas—often designated "brown tumors"—are actually benign giant cell tumors or osteoclastomas. Thus, the term giant cell tumor or osteoclastoma, rather than "giant cell sarcoma," should be used. Cyst formation frequently results when the weakened skeleton suffers a slight trauma, therefore Recklinghausen designated the bone disease he first described as osteitis fibrosa cystica generalisata.

Clinical Picture

The age of patients with Recklinghausen's bone disease is variable. Children are affected,[1,11] but only rarely. The frequency of the disease rises from the third decade on and is maximal in the sixth decade. Often the disease has lasted for many years before the correct diagnosis is made. Several cases are known in which the first symptoms of the disease were noticed 25 to 39 years before the hyperparathyroidism was finally discovered.[11]

Recklinghausen's bone disease cannot be diagnosed unless the biochemical syndrome of hyperparathyroidism—hypercalcemia, hypophosphatemia and hypercalciuria—is present, with the exceptions and limitations stated in previous paragraphs. When extensive bone lesions have developed, the alkaline phosphatase of the serum is always increased. The hypercalcemia not only causes complaints about fatigue, anorexia, constipation, nausea and vomiting, but also gives rise to electrocardiographic changes in the form of a shortening of the QT interval.

An apparently paradoxical sign has been observed by Barr, Bulger and Dixon.[7] They noted in their first patient with Recklinghausen's disease that, notwithstanding the bone pains, marked hypotonia of the muscles existed. Other clinicians have made the same observation, though infrequently. The muscular hypotonia must be related to the hypercalcemia, which decreases the tonicity of both striated and smooth musculature. Contrariwise, in hypoparathyroidism, the decrease of the serum calcium leads to increased excitability of the neuromuscular system, with resultant tetany. In most cases of Recklinghausen's disease, the presence of muscular hypotonia cannot be established because the tenderness of the skeleton limits the muscular activity and prevents careful examination.

Although nephrolithiasis and/or nephrocalcinosis are both frequently found in Recklinghausen's bone disease, the main symptoms and signs are skeletal in nature in the form of pains, pathologic fractures, deformities and occasional local swellings due to "brown tumors." Epulis occurs rather frequently. There is no increased caries of teeth, but the latter may be loosened or even fall out due to excessive bone resorption from the jaws (PLATE 11*b*). In the beginning, the true nature of the bone pains may not be recognized and the patient is often considered to suffer from neuritis, arthritis or fibrositis.

It must be repeated that in many cases of Recklinghausen's bone disease, only generalized resorption of bone due to osteitis fibrosa is found, without clear-cut giant cell tumors or cysts. On the other hand, in the presence of a giant cell tumor without generalized decalcification, the diagnosis of Recklinghausen's bone disease must always be considered.

At this point certain characteristics of giant cell tumors in general, occurring in patients without hyperparathyroidism, may be enumerated. A true giant cell tumor, or osteoclastoma, develops in the metaphyseal area of the long bones. An osteoclastoma often progresses towards the epiphysis and may ultimately occupy the larger part of the epiphyseal part of the bone. The diameter of the bone where the giant cell tumor is located is often increased. The cortex may be thinned to such an extent that it can be compared to an egg shell. Thus, pathologic

fractures are common. In a series of 101 cases collected by Williams et al., 68 per cent of the patients were between the ages of 21 and 39 years.[60] Nevertheless, several observations of the occurrence of giant cell tumors in patients under 20 years of age are found in the literature.

Eighty per cent of the giant cell tumors are found in the long bones. This lesion has a special preference for the bones which form the knee joint. Sixty per cent of the giant cell tumors are localized either in the distal epiphysis of the femur or in the proximal epiphysis of the tibia and fibula. However other long bones are far from immune, and giant cell tumors have even been encountered in the head of a metacarpal bone and as a great rarity, in a terminal finger phalanx.

Fourteen per cent of the lesions of the patients of Williams and associates were present in the ilium, sacrum, vertebral spine, ribs, and jaws. Eight of the apparent giant cell tumors studied by Williams were proved to be malignant. The large giant cell tumors of the head of the humerus especially are often true giant cell sarcomas.[60]

Lichtenstein[41] mentions that in recent years most of the giant cell tumors which have been submitted to him for an opinion had to be graded as 2+ or 3+ aggressive or potentially aggressive tumors. Most observers will agree with Lichtenstein's opinion. In such tumors local recurrence after surgical removal is frequent. The grade 3 giant cell tumors ultimately prove to be genuinely malignant.

No wonder that giant cell tumors nowadays are generally considered to be genuine neoplasms. Osteoclastomas cannot be considered to present merely a reactive tissue reaction after trauma or chronic irritation. This tendency to malignant degeneration reveals a fundamental difference between the giant cell tumors in patients who do not suffer from Recklinghausen's bone disease and the osteoclastomas which develop in hyperparathyroidism. The latter are never malignant.

The localization of the giant cell tumors is also of differential diagnostic importance. Osteoclastomas situated in the calvarium, maxilla or mandible are remarkably often a sign of hyperparathyroidism, as was first stressed by Barr, Bulger and Dixon, in 1930.[5] In 3 of the 12 cases reported in 1944 by Hellström and Wahlgren,[33], a tumor in the upper jaw was one of the initial manifestations of the disease. In every case where a giant cell tumor is found (PLATES 8b 10a) a careful determination of the serum calcium, serum phosphorus and urinary calcium excretion is necessary We have seen several cases in which a resection of part of the mandible had previously been performed for a giant cell tumor (PLATE 11a) Subsequently generalized resorption of bone was discovered (PLATE 8c) and the correct diagnosis of Recklinghausen's bone disease was made. If at the time, before the mandibular resection was performed, the necessary biochemical studies had been performed, the correct diagnosis would have been made before the operation. Since in cases of hyperparathyroidism the giant cell tumors recalcify very quickly after removal of the parathyroid adenoma, timely removal of this tumor would have saved the patient from a permanent mutilation of the face. In addition, this operation would have protected him from the progression of the osteitis fibrosa and the potential development of nephrocalcinosis.

Pathologic fractures occur very frequently often localized in the areas where giant cell tumors or cysts are present. Healing of such a fracture commonly leaves a malformation.

Roentgenologic Features

The roentgenologic findings clearly illustrate that Recklinghausen was correct when he so carefully selected the designation generalized osteitis fibrosa cystica for the disease he had discovered. At least in the later phases of the disease the skeleton in its entirety is affected, and the resorption of bone substance modifies the architecture of every bone examined. In some bones, however the results

of the lacunar resorption and the prolifera tion of fibrous tissue in haversian canals and bone marrow spaces may be more intense than in the rest of the skeleton. The structure of both the cortical and the cancellous bone is abnormal. In general the cortex is thinned, the bone marrow space is increased in di ameter, and the haversian canals are widened by the proliferating fibrous tissue. In many places osteolytic areas may be found within the cortex (Plate 8c), representing osteoclastomas, and/or bone cysts. In other in stances, the actively proliferating fibrous osteitis of the cancellous bone causes subcor tical osteolytic lesions. Elsewhere, the fibrous bone marrow impinges upon the cortex, and half moon-shaped indentations adjacent to the bone marrow space may result. This so-called scalloping may also be caused by the active subendosteal bone absorption within the cortex itself. In the terminal stages the absorption of bone may become so extreme that it is well nigh impossible to obtain sat isfactory roentgenograms. Kyphosis, pigeon breast and bowing of the legs are common signs in advanced stages. Collapse and frac ture of vertebrae, due to the softening of the spine, result in a marked reduction of the body length. Compression of the lumbosacral vertebral bodies by the elastic intervertebral disks leads to the formation of biconcave, so-called fish or hourglass vertebrae. In the thoracic spine the compressed vertebrae are wedge-shaped, with a maximum of compression present in the anterior part of the vertebral bodies. Pathologic fractures of the long bones usually result in considerable deformities.

Often the only roentgenologic sign of Recklinghausen's bone disease consists of generalized osteoclastic resorption of bone. In other cases giant cell tumors and bone cysts can be visualized on the roentgenograms. The osteoclastomas are mainly present in the skull (Plate 8a) jaw (Plate 11a) pelvis (Plate 7a) at the ends of long bones, meta carpals (Plate 10a) and metatarsals, and usually present as honeycomb-like giant cell tumors. However, the osteoclastomas sometimes are visualized as simple, *faintly de lineated*, cystlike lesions.

In such cases it may be difficult to decide before operation whether an osteolytic lesion is due to the presence of a bone cyst or an osteoclastoma. After removal of the parathy roid adenoma, the differentiation is easy the *osteoclastomas readily calcify* but the cysts remain unchanged for a long time, sometimes even for years. This can easily be understood because the osteoclastomas consist of proliferating masses of osteoclasts which proliferate under the influence of parathyroid hormone. The bone cysts, however, are non specific products of traumas and develop in all diseases with widespread bone absorption, irrespective of the etiology It also sometimes happens that the septate structure of the cystlike osteoclastoma appears only after operation. During the decalcifying stage of the disease the bone septa of the giant cell tumor may have been so thin that they could hardly be distinguished in the roentgenograms.

At the same time it should be stressed that other bone lesions such as plasmocytomas (Plate 35b), lipoid granulomas, reticulum cell sarcomas, metastases of clear cell car cinomas of the kidney and benign bone cysts of children occasionally cause an osteolytic lesion which at roentgen examination, may be highly reminiscent of a giant cell tumor

It may be repeated that the presence at roentgen examination of one or more honeycomb-like giant cell tumors in the bones of the skull, the lower or upper jaw, or the zygomatic bone, always strongly favors the diag nosis of Recklinghausen's disease. This holds true even when no generalized resorption of bone can be discovered (p. 70)

The importance of the radiologic picture of the skull for the diagnosis of Reckling hausen's bone disease *must be emphasized* (Plate 9a, b) The presence of a coarse meshed trabeculation and widespread granular or miliary areas of bone resorption is nearly characteristic. Actually, the washed out appearance *of both inner* and outer

tables may resemble old decayed wood. It is still more reminiscent of the results of the efforts of unreliable antique dealers who, at least in years gone by, peppered wood with bird shot in order to fake the small worm holes of antique, timeworn furniture. This typical roentgenogram of the skull alone sometimes permits the diagnosis of Recklinghausen's bone disease. The marked changes in the skull readily disappear after operation and, in some cases, the postoperative recalcification of the skull may even lead to a Paget like structure. We also have observed that after removal of the parathyroid adenoma, a marked generalized osteosclerosis of the skull developed.[83]

The roentgen picture of the hands in Recklinghausen's bone disease deserves special comment. In diseases where the function of the hands is impaired, e.g., rheumatoid arthritis, scleroderma, leprosy, etc., the inactivity of the metacarpal and phalangeal bones leads as a rule to extensive osteoporosis of the skeleton of the hands. In these diseases neurotrophic changes may also contribute to the resorption of bone. However in many other bone diseases with widespread resorption of bone, the carpals, metacarpals and phalanges remain normal. This is usually the case in multiple myeloma, postmenopausal osteoporosis, many cases of osteomalacia, widespread skeletal metastases, etc. In contrast, characteristic absorption of bone can be observed in the skeleton of the hands even in the early stages of hyperparathyroidism when the upper extremities are still actively used.

Whereas the scalloping of the cortex due to endosteal bone resorption has been known for a long time, the importance of subperiosteal bone resorption for the diagnosis of hyperparathyroidism has rightly been emphasized only in recent years.[84] One of the sites of predilection of periosteal bone resorption is in the skeleton of the fingers. The erosion of bone substance, which takes place just beneath the periosteum of the metacarpals and phalanges, has been described as being lacelike in character A moon-shaped defect in the marginal part of the phalanx results, especially marked in the margins of the middle phalanges of the fingers (Plate 10a) Resorption of bone substance in the tufts of the terminal phalanges also is commonly seen. This may lead to so-called destructive clubbing of fingers.[85,86] Clubbing in hyperparathyroidism can easily be distinguished from osteoarthropathy, as seen in bronchiectasis, congenital heart disease, and other maladies (p 183) the latter conditions do not lead to bony destruction of the terminal phalanges.

After removal of the parathyroid adenoma, regeneration and a complete reconstruction of the terminal phalanges readily occur and the clubbing of the fingers disappears. Subperiosteal resorption of bone nearly always occurs in the jaw The wall of the tooth sockets is formed by the subperiosteal bone of the jaw and presents a sharply defined line, the so-called lamina dura. That the lamina dura frequently disappears in the course of hyperparathyroidism (Plate 11c d) is yet another manifestation of subperiosteal bone resorption. The teeth themselves are not affected—caries is often practically absent. However the teeth easily fall out due to the resorption of the bone of the jaw Although the presence of subperiosteal bone resorption is always reason to consider the presence of hyperparathyroidism, the same skeletal anomaly is found in the widespread osteitis fibrosa, which occasionally befalls the skeleton of children and young adults with long drawn-out uremia. On the other hand, we have observed several cases of hyperparathyroidism where the lamina dura was still intact (Plate 11b)

Other sites of predilection for subperiosteal bone resorption are the areas adjacent to the lumbosacral articulations of the pelvis, the proximal metaphyseal part of the tibia (Plate 10c) and the part of the clavicle which is adjacent to the acromioclavicular joint (Plate 10b)

NEPHROLITHIASIS

In the presence of the nearly constant hypercalcemia and hypercalciuria, it is not sur

prising that 60 to 80 per cent of the patients with Recklinghausen's bone disease suffer from nephrolithiasis. Albright and associates recently demonstrated the presence of renal stones in 114 of 146 cases of hyperparathyroidism many of these patients had bilateral stones, while others showed recurring stone formation. Hellström found renal stones in 27 of his 50 patients with hyperparathyroidism.[34] In 17 of these cases, 29 operations for nephrolithiasis had been performed before the diagnosis of hyperparathyroidism was made. When the urine is alkaline—frequently due to infection of the urinary tract—the renal stones in hyperparathyroidism consist of calcium phosphate. Oxalate stones are found when an acid urine is excreted.

In guinea pigs, renal stones could be produced by the prolonged administration of parathyroid extract if, at the same time, the urethra of the experimental animals was clamped off daily for 7 to 12 hours. The hypercalciuria, combined with urinary obstruction, resulted in formation of renal stones in 3 of the 10 experimental animals.[62]

Around 1936, Albright and Bauer approached the problem of nephrolithiasis in hyperparathyroidism from a completely new point of view They considered that patients with nephrolithiasis might possibly suffer from unsuspected hyperparathyroidism without overt skeletal symptoms or signs. They soon collected the records of 11 patients admitted for nephrolithiasis alone, in whom the biochemical syndrome of hyperparathyroidism was discovered. In all these cases operation revealed the presence of a parathyroid tumor In the patients with minimal roentgenologic skeletal involvement and nephrolithiasis, the phosphatase content of the serum was still normal, although all the other biochemical signs of hyperparathyroidism were present. After continuing this investigation for a few years, the urologists in Boston estimated that three per cent of the patients who have renal stones suffer from hyperparathyroidism. This was confirmed by the urologists of the Mayo Clinic, where 18 proven cases of hyperparathyroidism were discovered in the course of 18 months among 950 patients who were admitted with the presenting sign of nephrolithiasis. In 1950, Beard and Goodyear reported that in two thirds of the Mayo Clinic cases of renal lithiasis caused by hyperparathyroidism, only one single stone was present.[9]

The observation in this part of the world that renal stone formation often precedes the presence of bone lesions may be connected with dietary factors.[8] The markedly negative calcium balance in hyperparathyroidism will lead to a rapid depletion of the skeletal calcium should the calcium intake be low If, however large amounts of calcium, phosphate, and vitamin D are ingested with the food, the resorption of bone will be delayed. Milk is a nutrient rich in calcium and phosphorus. Since nearly all the milk in the United States today is irradiated,[63] this nutrient always contains large amounts of vitamin D (p 36) It is evident, therefore, that in an American milk-drinking patient with hyperparathyroidism, the high calcium, phosporus and vitamin D intake will easily lead to nephrolithiasis, whereas at the same time the skeleton is protected. In Europe, where milk is not a popular nutrient among adults, hyperparathyroidism will more frequently result in the development of Recklinghausen's disease.

For the diagnosis of renal stones due to hyperparathyroidism, an increased calcium excretion in the urine on a calcium-poor test diet is just as important as an increased calcium and decreased phosphorus content of the serum. The phosphatase value remains normal as long as the skeleton is not involved.

A strongly positive Sulkowitch test in a patient with renal stones who is on a calcium-poor (Bauer Aub) diet is at least reason to suspect the possibility of hyperparathyroidism. A consistently weak positive test is usually an important point against the diagnosis of hyperparathyroidism.

Nevertheless, as always, caution is necessary In 1938 we found that hypercalciuria is

relatively frequent among patients with oxalate stones. Using the test diet mentioned above (p. 66) which contained 415 milligrams of calcium, patients without renal stones excreted on an average 165 milligrams and never more than 250 milligrams in the 24 hour urine. Among 14 patients with calcium oxalate stones 6 patients excreted per 24 hours 252 275 283 292, 332, and 401 milligrams of calcium, respectively The serum calcium of these 6 patients was normal. It follows that even in patients with nephrolithiasis in whom hyperparathyroidism can be excluded, high urinary calcium excretion is relatively common.[44] This has been confirmed by Albright et al. who nearly always found hypercalciuria in patients with rapidly growing or with frequently recurring renal stones.[14] Thus, for the diagnosis of renal stones without skeletal lesions, due to hyperparathyroidism, the presence of not only hypercalciuria and hypercalcemia but—in the presence of normal renal function—hypophosphatemia, is required. The diagnosis of renal stones due to hyperparathyroidism without skeletal involvement is often difficult and, in such patients, a negative parathyroid exploration cannot always be avoided.

NEPHROCALCINOSIS

Hyperparathyroidism leads not only to the development of renal stones but also to the impairment of renal function and ultimately to renal failure. When hypercalcemia and hypercalciuria last for a long period, calcium precipitates in different organs. These so-called calcium metastases are frequently found in the kidneys, but are also present in the media of arteries, the myocardium, the lungs, the mucous membranes of the stomach, bronchi and other organs. Recently a patient with hyperparathyroidism and symmetrical cerebral calcifications involving the basal ganglia has been reported.[45]

The presence of calcium deposits in the kidneys is designated nephrocalcinosis, whether the calcification can be discovered by gross or only by microscopic examination. Gross nephrocalcinosis in hyperparathyroidism can often be visualized on the roentgenograms of the kidneys in the form of calcifications in the medullary part of the kidney in the area of the renal pyramids and the renal pelvi (PLATE 6a) On the intravenous pyelograms, the calyces always enclose the tips of the calcified pyramids. The cortex remains free of macroscopic calcific precipitations.[47, 48] Neph rocalcinosis is not specific for hyperparathy roidism, it may also be seen in other conditions, e.g., patients who for many years have been taking large quantities of alkali and calcium for the treatment of a peptic ulcer (p 94) tubular acidosis with or without previous treatment with sulfa drugs (p. 48) hypervitaminosis D (p. 51) sarcoidosis (p. 101) and other conditions (p. 221) In all of these diseases, the calcium deposits are only located in the medullary part of the kidn and cannot be distinguished roentgenograp ically from the nephrocalcinosis occurring i hyperparathyroidism. Arons and associates have recently called attention to the differ ent localization of the nephrocalcinosis which is encountered (though rarely) in patients with chronic glomerulonephritis. In this condition the calcium deposits involve mainly the renal cortex.

The size of the calcific deposits in nephrocalcinosis varies. They are usually "millet sized, but they may grow until cauliflower like deposits ultimately result. Contrariwise, in other cases, these deposits can be reco nized only with difficulty appearing on th roentgenograms as a fine stippling There i no correlation between the size of the calcium deposits in nephrocalcinosis and the intensity of the kidney damage. Even microscopic calcium deposits in the kidneys may cause fatal uremia.[46] Only thirteen cases of nephrocalcinosis in hyperparathyroidism appeared in the literature between 1903 and 1934 but in the recent reviews many more cases are mentioned. Askanazy's famous case,[2] reported in 1903 showed signs of interstitial nephritis with many small areas of calcification in the cortex and medulla. Among 12 patients with hyperparathyroidism, Hellström and Wahl-

gren found neither calcifications nor concrements in 3 cases, calcification plus concrements in 4 cases, and concrements but no calcifications in 2 cases.[61]

In the early stages of nephrocalcinosis, microscopic calcium deposits develop first in the lumen and then in the wall of the convoluted and the collecting tubules. Later, calcium precipitates in the interstitial tissue of the renal pyramids. Necrosis frequently develops in the areas of calcification. The tubules may be dilated or collapsed, ultimately, the glomeruli degenerate to hyaline masses and the entire structure of the kidney is completely disorganized. Such calcium precipitations were nearly always found in the kidneys of dogs treated for several weeks with parathyroid extract. In rats given parathyroid extract over long periods, obstruction of the tubules by calcium deposits led to atrophy and dilitation of groups of nephrons, with eventual renal failure.

Signs of kidney damage can be elicited in almost all cases of hyperparathyroidism, even if albuminuria, increase of blood urea nitrogen, nephrolithiasis, or roentgenologically visible nephrocalcinosis are absent. In the majority of patients with hyperparathyroidism, the concentration power of the kidneys is impaired and the specific gravity of the urine secreted during a concentration test remains well below the normal levels.[62] This hyposthenuria indicates that in all cases of hyperparathyroidism, extensive microscopic precipitation of calcium must have occurred in the kidneys, even if no proteinuria or other overt signs of renal damage are present. In the future, puncture of the kidneys of patients with hyperparathyroidism will certainly be used to obtain information about the extent of the nephrocalcinosis.

Whether such microscopic nephrocalcinosis is also the cause of the hypertension found in many cases of hyperparathyroidism remains to be seen. In the first stage of nephrocalcinosis only the tubules are damaged by the precipitation of calcium. Therefore, in initial cases of nephrocalcinosis the tubular function, i.e., concentration, is already damaged, but the glomerular function, i.e., glomerular filtration, can remain normal. In the later stages the glomerular filtration suffers because the obstruction of the tubules by the precipitated calcium causes glomerular dilatation. In patients with marked renal damage due to nephrocalcinosis, the uremia becomes progressively worse, even after successful removal of the parathyroid adenoma(s) Favorable exceptions occur a few cases of hyperparathyroidism are known where, after operation, the glomerular function returned to normal but the tubular function remained poor Only rarely does the tubular function actually improve and the specific gravity of the urine return to normal after operation.

In patients with hyperparathyroidism and widespread microscopic nephrocalcinosis not detectable on the roentgenograms, the clinical picture of hyperparathyroidism may consist only of renal failure.[63] Thus, the diagnosis of hyperparathyroidism must be considered in every case of chronic renal failure with hypercalcemia, even in the absence of the main roentgenologic evidence for diagnosis—skeletal changes, renal stones, gross nephrocalcinosis. The diagnosis is facilitated by the well-known experience that hypercalcemia is rare in chronic uremia, except in multiple myeloma with Bence Jones proteinuria.

The danger of progressive nephrocalcinosis in hyperparathyroidism is well illustrated by the history of a patient who was operated on for a renal stone in 1943 At that time the possibility of hyperparathyroidism was not considered. He was well for six years, when a new renal stone was found. He again underwent surgery, but developed uremia postoperatively Only then were the serum calcium and phosphorus examined in the presence of marked hypercalcemia, the diagnosis of hyperparathyroidism was mandatory He died three weeks after the second operation. At autopsy a small chief cell adenoma was found. There was extensive calcification

of the renal tubules, together with calcinosis of lungs, heart, stomach, and thyroid. The skeletal anomalies were negligible.[83]

It must be added that our patients with hyperparathyroidism who originally sought advice for nephrolithiasis without marked impairment of the kidneys, have remained completely well after removal of the parathyroid adenoma. On the other hand, we also have observed that impairment of renal function present before operation became worse after removal of a parathyroid adenoma. The ultimate success of the operation in hyperparathyroidism depends upon the extent of renal damage present before the operation.

One of our patients was operated on in 1934 for a very severe form of Recklinghausen's bone disease. At that time there was only a trace of protein in the urine, but the blood urea nitrogen was increased to 31 mg per cent, the nonprotein nitrogen, to 54 mg per cent. The PSP test revealed only 23 per cent excretion in two hours. After the operation his skeleton improved remarkably. The biochemical syndrome returned to normal and his renal condition improved somewhat, although it never became completely normal. In 1947 his blood urea nitrogen was still 30 mg per cent. In 1949 this value increased to 60 mg. per cent. He died from uremia in 1950, 16 years after the removal of the parathyroid adenoma. Rienhoff found that 9 of 29 patients operated on for hyperparathyroidism died from hypertension and uremia between three and eleven years after operation.[84] Parsons[81] operated on 32 patients with hyperparathyroidism. Nine of these had neither renal stones nor renal damage. 17 had renal stones with a normal or only slightly impaired renal function. Only one of these 26 patients died but in this case a parathyroid carcinoma had been found. The other 25 were all well, some of them 10 years after operation. However the 6 patients who had marked impairment of kidney function before operation all died within a few years after the intervention.

Johnson[85] observed progressive uremia after parathyroidectomy in a patient with a parathyroid adenoma who at the same time had a horseshoe kidney. Recently we saw such an unfavorable course in a patient with four parathyroid adenomas and polycy[stic] kidneys.

Hellström emphasized the prevalence [of] renal damage in patients with hyperpara[thyroidism] due to generalized parathyroid hyperplasia. Two of his 7 cases of primary hyperplasia died of uremia. 2 others became "severely disabled" by hypertension. However, of Hellström's 37 patients operated on for a single parathyroid adenoma, only three ultimately died of uremia and 2 of cerebral hemorrhage, due to progressive hypertension.

Occasionally even a patient with hyperparathyroidism and clear-cut renal damage does well after parathyroidectomy. In 19[36] we observed a patient with an osteoclastom[a] of the skull and discrete skeletal lesions. Th[e] biochemical analysis of serum and urine con[-]firmed the diagnosis of hyperparathyroidism. Before operation she was found to have albuminuria and a blood pressure of 175/110. The serum nonprotein nitrogen had risen to 52 mg per cent, and during a PSP test only 20 and 23 per cent of the dye was excreted. Fine calcium stippling in the renal medulla was visualized on the roentgenograms. She was operated on in 1936 and was still living in 1950, at which time her blood urea nitrogen was only 28 mg per cent, although her blood pressure had further risen to 270/140.[86]

In this connection, it may be emphasized that the generalized osteitis fibrosa with decalcification, the multiple giant cell tumors, and the bone cysts must constitute a late stage of hyperparathyroidism. In earlier stages the destruction of the skeleton may not yet be visible on the roentgenograms, notwithstanding severely disturbed calcium and phosphorus metabolism.

The skeleton of an adult contains 1000 to 1500 grams of calcium. Even in severe cases of hyperparathyroidism, the daily loss of calcium hardly ever exceeds 0.5 gram—at

the most, 1 gram. At least 25 to 40 per cent of bone substance must have disappeared before the decrease of the calcium content of the skeleton can be appreciated on the roentgenograms (p. 12). Thus, a few years must elapse before the excess of calcium and phosphorus excreted in the urine in hyperparathyroidism will have caused the formation of clear-cut roentgenologic skeletal destruction. In the meantime, nephrolithiasis and nephrocalcinosis may already have developed.

The progression of the bone lesions can always be stopped by the removal of the parathyroid adenoma. After this operation, rapid repair of the osteitis fibrosa and calcification of the osteoclastomas is the rule. Unfortunately, after parathyroidectomy the function of the damaged kidney may deteriorate progressively, even if a spectacular clinical cure of the skeletal lesions is obtained. These considerations militate in favor of early recognition of hyperparathyroidism and subsequent operation.

HYPERPARATHYROID CRISIS OR ACUTE HYPERPARATHYROIDISM

Analogous to the thyrotoxic crisis which may develop in the course of Graves's disease, a hyperparathyroid crisis, also named acute hyperparathyroidism or parathyrotoxicosis,[21] may occur in a patient with a parathyroid adenoma. During such a parathyroid crisis large amounts of parathyroid hormone are poured into the circulation and an excessive hypercalcemia ensues. James and Richards[86] recently reviewed 14 cases of acute hyperparathyroidism reported in the literature and added a new case. Twelve cases were due to a parathyroid adenoma, [illegible] to generalized hyperplasia of the parathyroids and 1 to administration of excessive doses of parathyroid extract (p. 81). Most cases of acute hyperparathyroidism represent an exacerbation of chronic parathyroid hyperfunction due to an adenoma. A few observations have been reported of patients who suddenly developed the complete syndrome of acute hyperparathyroidism without any skeletal, renal, or other manifestations of the chronic disease.

The symptoms and signs of acute hyperparathyroidism consist of gastrointestinal, central nervous system, and renal manifestations. Nausea, persistent vomiting, abdominal pains and obstipation develop. These symptoms are associated with fever, tachycardia, oliguria and vasomotor paralysis. The mental signs consist of listlessness and lethargy. Occasionally a patient has been delirious. One of the patients described exhibited a peculiar listlessness, weakness and apathy which was designated by the psychiatrist as an agitated depression. The severity of the agitation was commensurate with the intensity of the hyperparathyroidism. The abrupt increase of the serum calcium causes an acute calcium infarction and necrosis of the renal tubules. This rapidly leads to oliguria and increasing uremia. Although other explanations have been mentioned, this acute renal failure is probably the reason for the high serum phosphorus which is regularly found in these patients. Due to this sudden cessation of the renal function, acute hyperparathyroidism often leads to a fatal termination. At autopsy widespread calcium metastasis in kidneys, heart, lungs, stomach, and the media of the arteries are found, together with multiple venous thromboses.[87]

In at least three cases, removal of the parathyroid adenoma, performed as an emergency operation, saved the life of the patient. Recently we had the same gratifying experience. Two of these patients were in a moribund condition prior to operation. When the condition of the patient is so poor that operation cannot be undertaken, the administration of a chelating agent such as di-sodium ethylenediamine tetraacetate (EDTA) should be considered. It seems possible that this medication might improve the condition of a patient with acute hyperparathyroidism sufficiently to permit the undertaking of removal of a parathyroid adenoma. Cortisone, which blocks the absorp-

tion of calcium from the intestine, should also be tried.

The symptoms and signs of acute hyperparathyroidism are mainly the result of the excessive hypercalcemia. The same syndrome is therefore observed when hypercalcemia is caused by acute and widespread skeletal metastases of malignant lymphomas or anaplastic carcinomas, occasionally even in multiple myeloma. Comparable "chemical uremia" may also be caused by acute and complete immobilization in severe forms of poliomyelitis and by the application of extensive plaster casts (p. 26).

GASTROINTESTINAL SYNDROME

In hyperparathyroidism, marked hypercalcemia does not always give rise to all symptoms and signs of acute hyperparathyroidism. In certain instances the hypercalcemia leads only to complete anorexia, nausea, pernicious vomiting, constipation, and obstipation, without causing clear-cut renal or mental manifestations. In such a patient skeletal anomalies may well remain in the background. Under these circumstances it will be possible to recognize the presence of hyperparathyroidism as the cause of gastrointestinal complaints only by calcium and phosphorus determination of the serum. Hyperparathyroidism with uncontrollable vomiting—an outstanding sign in experimental hypercalcemia, too—was first described by Morelle and Beyerinck, both in 1932.[44] In both observations the skeletal lesions were minimal.

In Morelle's patient an intestinal obstruction complicated by continuous vomiting had been diagnosed. Marked hypercalcemia, which was discovered by accident, ultimately led to the correct diagnosis of hyperparathyroidism. After removal of a parathyroid adenoma the gastrointestinal disorders improved rapidly. Beyerinck's patient with primary hyperplasia of all four parathyroids died of pernicious vomiting and hypercalcemia.

Of even greater clinical importance is the observation of Rogers et al.[26] They reported two patients with fatal acute hyperparathyroidism in whom a duodenal ulcer was found at autopsy. In one patient a chief cell adenoma of the parathyroid was present, in the other there was a clear-cell hyperplasia of all parathyroids, nine in total. The combined weight of these nine parathyroids was 20.32 grams. In both cases metastatic calcifications in the kidneys and other organs were present. Since then, simultaneous occurrence of hyperparathyroidism and peptic ulcer has been reported so frequently that the combination of these two ailments can hardly be purely coincidental. Haynes reviewed all the cases of hyperparathyroidism of the Mayo Clinic[16] and found either recent or previous objective evidence of peptic ulcer in 24 per cent of these patients. Some had undergone a stomach operation. At the Johns Hopkins Hospital 15 per cent,[24] and at the Massachusetts General Hospital 8.8 per cent[14] of the patients with hyperparathyroidism had associated peptic ulcers. Hellström encountered 7 duodenal ulcers but no stomach ulcers among his 50 cases of hyperparathyroidism.

It is remarkable that a peptic ulcer has little tendency to heal as long as hyperparathyroidism persists.[16,44] In such cases the ulcer crater may rapidly disappear after removal of the parathyroid adenoma. About 50 per cent of the patients with hyperparathyroidism and ulcer complaints became free of pain after parathyroidectomy.

Administration of Sippy powders containing calcium carbonate to a patient with a duodenal ulcer and hyperparathyroidism may cause dangerous complications. In patients with a parathyroid adenoma such large quantities of calcium salts may lead to the development of nephrocalcinosis or even to the dangerous syndrome of acute hyperparathyroidism.

The coexistence of a duodenal ulcer in hyperparathyroidism may easily be confused with another unrelated syndrome, the metastatic calcification and nephrocalcinosis

which may develop from long-standing medical treatment of peptic ulcer (p. 94)

DIABETES INSIPIDUS–LIKE SYNDROME

In hyperparathyroidism, marked polydipsia and polyuria may increase the daily urinary output to 12 and 13 liters. When in such patients the parathyroid adenoma is removed, polyuria and polydipsia disappear immediately. In such cases the diagnosis of true diabetes insipidus due to damage of the posterior lobe of the pituitary gland has often been seriously considered. There is, however, no evidence for the assumption that disturbances in the posterior pituitary occur in hyperparathyroidism. In fact, in 7 cases of generalized hyperplasia of the parathyroids, Albright found a normal amount of pituitary hormone in the urine. Recently it has been emphasized that pituitary hormones, especially growth hormones, increase the phosphate content of the serum. The latter electrolyte change allegedly could stimulate parathyroid activity and it was assumed that in this way the pituitary might influence the parathyroids.[4] Here, too the experimental evidence available does not seem conclusive.

It has been speculated that just as the excretion of glucose in diabetes mellitus is necessarily accompanied by polyuria, so in hyperparathyroidism the hypercalciuria could perhaps be responsible for the polyuria. The polyuria could then be explained by the assumption that the elimination of excessive amounts of calcium in the urine requires the excretion of large amounts of water. As a matter of fact, the term "calcium diabetes" has been used to designate this condition. The oliguria, which nearly always sets in after removal of a parathyroid adenoma, would then depend upon the cessation of the hypercalciuria. This explanation of the polyuria in Recklinghausen's disease is probably not correct. In the rare patients with hyperparathyroidism without hypercalciuria, the postoperative oliguria was just as marked as in other patients who had preoperative hypercalciuria.

In this connection it must be stressed that injections of parathyroid extract have been used successfully to induce diuresis in patients with cardiac failure, oliguria and edema. It is important to note that during diuresis due to parathyroid extract, the calcium excretion in the urine is not increased. Thus, parathyroid hormone apparently has a direct stimulating influence upon the renal function, probably by increasing glomerular filtration. This increased filtration must be the major factor causing the polyuria in hyperparathyroidism, there is no reason to continue the term "calcium diabetes."

In 1949[43] we observed a patient in whom polydipsia and polyuria had existed for at least seven years. The urge to urinate was so intense that he had difficulty in controlling his bladder function and suffered frequently from urinary incontinence. The urine never showed the presence of protein, but during the last year it had occasionally contained hyaline casts. Severe constipation had set in, although previously he had always had a normal elimination and had never needed a laxative. His appetite had diminished and occasionally he noticed headaches and nausea. For the last year his blood pressure had been rising and had recently varied between 155/90 to 200/100 mm.

In 1932 a small calcium oxalate stone had been removed from the left kidney. Determinations of blood urea nitrogen and glucose had been made at irregular intervals since 1938 and until shortly before admission had always been normal. Only during the last month had the nonprotein nitrogen and urea nitrogen of the blood risen slightly. Thus, a certain amount of renal damage was evidently present. This finding practically excluded a non-complicated diabetes insipidus. At the same time the polyuria and polydipsia could not be explained by renal damage alone. Protein was never present in the urine and the urinary sediment was practically normal. Furthermore, when renal

insufficiency leads to severe polydipsia and polyuria, the blood urea nitrogen is usually very high.

Examination of serum and urine revealed the presence of hyperparathyroidism. The calcium content of the serum was 18.3 mg per cent, the inorganic phosphorus 3 mg per cent, and the alkaline phosphatase was increased to 23 King Armstrong units per 100 cc. On a calcium-poor diet an average of 730 milligrams of calcium were eliminated per 24 hours in the urine. The history including removal of a small renal stone in 1932 fitted well with the syndrome of hyperparathyroidism.

Gross nephrocalcinosis could not be visualized on the x rays but the microscopic calcium precipitation had evidently been sufficiently extensive to impair renal function. The phenolsulphonphthalein test showed that only 11 per cent of the dye was eliminated within the first hour, and 10 per cent within the second hour. Careful x ray examination failed to elicit any signs of abnormal bone resorption.

The patient was operated on and a parathyroid adenoma the size of a walnut was removed. The polydipsia and polyuria disappeared immediately after the operation. Two months later the calcium of the serum was 10 mg per cent, the inorganic phosphorus, 2.6 mg per cent, the alkaline phosphatase, 7 King Armstrong units per 100 cc., and the blood pressure, 158/100. Seven years after operation the patient was completely well and led a normal active life.[44] His blood pressure had returned to normal.

MENTAL DEPRESSION

In some cases of marked hypercalcemia due to hyperparathyroidism, severe disturbance of the mental balance may overshadow the signs and symptoms due to damage of the skeleton or any other organ system. In fact, patients with hyperparathyroidism may demonstrate such markedly psychotic behavior[11,45] that an admission diagnosis of melancholia or paranoia may seem justified.

In 1947 a woman 54 years old was admitted with the following history.[45] She had always been in good health until about eight months prior to admission, when fatigue and loss of strength gradually developed. Whereas she had always been a normal and good-natured woman, now minor events would upset her and she often would cry for no apparent reason. Anorexia and severe constipation set in and persisted unabated. Gradually she had become bedridden because of her marked weakness.

At the time of admission her depression was not agitative in nature. She suffered from persecution complexes and believed that patients all over the ward were whispering about her saying she was crazy and dirty. She also developed a notion that she was going to have her arms and legs amputated. This fear grew out of her failure to understand why her arms and legs had been x rayed several times. The psychiatrists were of the opinion that the diagnosis of involutional melancholia or involutional paranoid state with depression was in order. In the course of the second week of her hospital stay she often became very agitated. The delusions of persecution continued. Now convinced that everybody tried to poison her she had to be coaxed to drink water because she declared the water tasted as though it were tainted. She also asked continuously why everyone was so hostile toward her.

Laboratory findings pointed to the presence of hyperparathyroidism. The calcium content of the serum was found to be 16 mg per cent, the inorganic phosphate, 1 mg. per cent, and the alkaline phosphatase 31 King Armstrong units. During the concentration test the specific gravity of the urinary specimens usually varied between 1.008 and 1.010. The blood urea nitrogen was 9 mg per cent. X ray examination revealed an advanced resorption of bone of the spine, long bones, skull, and pelvis, with narrowing of the cortices of hands and long bones. In the skull a pebbled and mottled appearance was visualized. The periodontal lamina dura was

absent. There was no definite collapse of any of the vertebrae and no osteoclastomas or cystic changes were observed.

The mental confusion of the patient made it impossible to put her on a Bauer Aub diet and to collect 24 hour urine specimens. However, on a calcium-poor diet all urine specimens which could be collected showed a heavy precipitate after addition of the Sulkowitch reagent. This indicated that even on a calcium-poor diet the urine contained considerable amounts of calcium.

At operation a parathyroid tumor 1.50 centimeters long and 0 75 centimeter thick was found between the vertebral column and the esophagus. Another small parathyroid gland was discovered at the right side and three small parathyroids at the left side. After operation the patient received parathyroid extract subcutaneously and calcium intravenously Nevertheless, the Sulkowitch reaction of the urine became completely negative, the calcium of the serum gradually decreased to 6 2 mg per cent, and Chvostek and Trousseau signs became positive. During this period the patient's mental state deteriorated and she sank into a stuporous condition. After the amount of calcium gluconate given intravenously was increased, the signs of hypocalcemia disappeared, and from then on her condition improved gradually When the patient was discharged six weeks after the operation, the amount of calcium excreted in the urine during three days on a Bauer Aub diet totaled 241 milligrams, that is, low normal. The psychiatric condition had also improved, although she still was hallucinating. At times she was apt to become tense and excited, but on the other hand, she ultimately realized that everybody had been treating her with kindness.

Two years after operation she showed continued good health. She had gained considerable weight. At that time the blood urea nitrogen was 17 mg per cent, the serum calcium, 10 2 mg per cent, the inorganic phosphorus, 2.3 mg per cent, and the alkaline phosphatase, 15 King Armstrong units per 100 cc. The blood pressure was 170/100 X rays revealed that only in the calvarium and along the intervertebral edges of the vertebral bodies had a slight degree of reossification taken place.

It was fortunate that the correct diagnosis of hyperparathyroidism had been made before admission to the hospital. Otherwise, this patient might well have been admitted and treated as a purely psychiatric problem.

The close relationship between hypercalcemia and mental signs, especially lethargy and mental confusion, was clearly demonstrated by the old observation of Löwenburg and Ginsburg[48] who studied a boy of five years who erroneously received 100 units of parathyroid extract for six successive days. On the first day vomiting and listlessness and on the fourth day extreme mental depression set in. On the fifth day his temperature rose to 103° There was marked apathy and areflexia. The next day the serum calcium was 19 6 mg per cent, the serum phosphorus, 4 4 mg per cent. Then the error was discovered, the parathyroid extract was discontinued, and the patient recovered rapidly

TREATMENT

Exceptional cases have been reported where a spontaneous partial cure of hyperparathyroidism seems to have occurred. Howard and associates reported one such case where infarction of the parathyroid adenoma with sudden outpouring of large amounts of parathyroid hormone led to an attack of acute hyperparathyroidism of short duration.[36] Thereafter all biochemical signs returned to normal and at operation the entire parathyroid adenoma was found to be necrotic. In two cases which at autopsy appeared to represent a healed stage of Recklinghausen's disease, one and two parathyroid adenomas respectively were still present.[67]

Several authors have observed that under influence of medication with calcium, phosphorus and either vitamin D or ultraviolet

irradiation, recalcification of the skeletal lesions can be obtained. It must be emphasized that in such cases the metabolic anomalies of hyperparathyroidism continued unabated. Therefore, even if the condition of the skeleton improves remarkably, this "dietary treatment" of Recklinghausen's bone disease is not without grave danger. The augmented intake of calcium, phosphorus and vitamin D leads to a still greater increase of the already excessive excretion of calcium and phosphorus in the urine, resulting in both progressive nephrocalcinosis and the formation of renal stones. The dangers of renal involvement and renal failure far exceed the advantage of the improvement of the bone pains and of skeletal erosion.

The following observation confirms the older reports[67] that under the influence of calcium, phosphate and vitamin D administration, a miraculous improvement of the skeletal changes of patients with Recklinghausen's bone disease can be obtained. At the end of 1955, a woman of 27 years was admitted who, in 1954, presented all the signs of a combination of renal insufficiency and hyperparathyroidism. There was widespread skeletal absorption, and multiple osteoclastomas could be visualized at roentgen examination. She then received daily doses of calcium and phosphate together with 50 000 units of vitamin D for nine months. At admission in 1955 roentgen examination revealed that a complete recalcification of the skeleton of skull and extremities had been obtained. In addition a dense calcification of the giant cell tumors had taken place (PLATES 7a, 8a). In short, as far as the skeleton was concerned, the repair under influence of dietary treatment was exactly the same as it would have been after removal of the parathyroid adenomas. Unfortunately, at the same time the condition of the kidneys had deteriorated considerably and frank uremia with high urea nitrogen, creatinine, uric acid, inorganic phosphorus and severe pruritus of the skin had developed. Notwithstanding this desperate condition, operation was decided upon and two chief cell adenomas were found. It was impossible to prolong the surgical intervention and to search for other adenomas. The serum calcium did not decrease postoperatively and the course of the uremia was relentlessly progressive. The patient died a few months later. At autopsy two more genuine parathyroid adenomas were discovered.

As mentioned on page 67, in the later stages of Recklinghausen's disease a certain amount of osteomalacia may be superimposed on the manifestations of hyperparathyroidism. Thus, improvement of generalized fibrocystic osteitis obtained by the administration of calcium, phosphorus, and vitamin D can be ascribed—at least partly—to the improvement of the avitaminosis D which complicates the hyperparathyroidism.

It is hardly ever possible to determine by palpation before operation where the parathyroid adenoma is located. Often the palpation is completely negative. Even a tumor which moves with swallowing, felt in the thyroid area of a patient with hyperparathyroidism, at operation usually proves to be a thyroid adenoma. In such cases the parathyroid tumor is then found at a completely different site.

In many instances of hyperparathyroidism, it has been possible to visualize the parathyroid adenoma on roentgenograms.[66] Wyman and Robbins[71] reported that in 34 surgically proven parathyroid adenomas, 20 could be recognized by roentgen examination. Only in rare cases could a soft mass be made out. Usually the presence of a parathyroid adenoma manifested itself in the form of an indentation of the esophagus (PLATE 10d) and/or of the trachea.

The technic of parathyroid exploration has been described in many excellent articles[14,46] and will not be discussed here. The most important point is the perfect control of hemorrhage. If no parathyroid tumor is found on the posterior side of the thyroid gland, the operation should not be terminated, for the tumor may have developed

an aberrant parathyroid (p 60) Every vascular pedicle starting from the inferior thyroid artery and directed downward toward the mediastinum must be carefully dissected. Such a branch often represents the blood supply of a mediastinal parathyroid adenoma (p. 63)

A parathyroid tumor hidden within the depth of the thyroid gland cannot be discovered during operation When at operation no parathyroid adenoma has been found, even after dissection of the mediastinum, subtotal resection of the thyroid gland must be performed before the exploration is terminated. Then the resected portion of the thyroid must be examined microscopically in order that a deeply imbedded parathyroid adenoma not be overlooked.

Irradiation of the parathyroid adenoma has been tried in a number of cases but with only questionable results. None of the reports of recent years would indicate that roentgen ray treatment has a favorable influence upon hyperparathyroidism.

It follows that in all cases of hyperparathyroidism, parathyroid exploration will be necessary If at all possible, the parathyroid adenoma should be found during the first operation. A parathyroid exploration nearly always leads to postoperative adhesions. The latter may cause well nigh unsurmountable technical difficulties if a second surgical search for an adenoma has to be performed. Even when at operation an apparently characteristic yellowish brown "parathyroid" tumor is discovered the intervention should not be terminated until a frozen section of the specimen has been examined. It is remarkable how often on histologic examination the specimen is proved to consist of thyroid or lymphatic tissue! When, after successful removal of one parathyroid adenoma, the calcium content of the serum fails to fall below normal, a second exploration is indicated.

When a generalized hyperplasia of all four parathyroids is present, three of the hyperplastic parathyroids must be completely removed and the fourth gland should be partially resected. There is a growing tendency to remove more and more of the fourth remaining hyperplastic parathyroid gland. In his recent operations for primary generalized hyperplasia of the parathyroids, Cope left only 80 milligrams of parathyroid tissue behind At least one such patient did well. But unless the vascularization of the parathyroid tissue left in the body is sufficient, fatal tetany may result.

Repeatedly, in cases of Recklinghausen's disease where no parathyroid adenoma had been discovered during operation, a tumor has been found at autopsy

Removal of one or two normal parathyroids in cases of hyperparathyroidism is of no avail and is even dangerous. If a parathyroid adenoma is present elsewhere, the degree of hyperparathyroidism is not modified by the removal of two normal parathyroids. If then, at a subsequent operation, the adenoma is at last found, the removal of the tumor may result in fatal tetany Such a patient may have possessed only three parathyroids, in one of which tumor formation had taken place.

After excision of a parathyroid adenoma the hypercalcemia quickly changes to subnormal values. In some cases, the decrease of the serum calcium continues and, ultimately, after one or two weeks results in tetany The premonitory signs of tetany consist of numbness and tingling all over the body especially in the toes. Stiffness of the fingers and changes of the sensorium, usually depression, are also danger signals. As long as Chvostek's sign is negative the serum calcium has not decreased below 7 mg per cent and the development of tetany is not imminent. To explain the postoperative hypocalcemia, it has been suggested that the presence of a parathyroid tumor might lead to atrophy of the other parathyroids. This would be analogous to the cases of an unilateral adrenal cortical tumor in which the other adrenal gland is usually atrophied.

However examination of one of the remaining parathyroid glands, found along with the adenoma, has always revealed that this gland was histologically normal and showed no sign of atrophy Moreover insufficient secretion of parathormone can hardly be the reason for the postoperative tetany in Recklinghausen's disease. In one case, even daily injections of 100 units of parathyroid extract were not able to modify the hypocalcemia that had occurred after removal of a parathyroid tumor In this patient, immediate improvement was obtained by injecting calcium chloride intravenously

Damage to the other parathyroids during operation can also be excluded as an explanation for the postoperative hypocalcemia. Our original explanation[41,43] still remains the most probable one after removal of the parathyroid tumor calcium is so avidly absorbed by the decalcified skeleton that hypocalcemia results. When after a few weeks a certain amount of skeletal recalcification has taken place, the remaining parathyroids can maintain a normal calcium balance. This opinion is supported by the fact that the more extensive the skeletal resorption and the higher the preoperative alkaline phosphatase of the serum, the greater the likelihood of postoperative tetany

Since nowadays nearly all cases of hyperparathyroidism are operated on in a relatively early stage, before extensive resorption of bone has taken place, postoperative tetany has become a rarity In modern times large doses of calcium salts by mouth (if necessary calcium gluconate intravenously) given after the operation, are nearly always sufficient to keep the hypocalcemia within reasonable limits.

After removal of a parathyroid adenoma transitory oliguria frequently occurs. This may last for several days. Most, if not all, patients with Recklinghausen's disease have damaged kidneys, as manifested by isosthenuria. If in such patients the daily urinary output diminishes to a few hundred cubic centimeters or less, transient uremic signs and an increase of the blood nonprotein content may easily follow

The frequent presence of polyuria in hyperparathyroidism due to increased glomerular filtration has already been discussed (p 79) After removal of the parathyroid tumor only a normal amount of parathyroid hormone reaches the glomeruli—much less than during the years of hyperparathyroidism. It takes a few days before the kidneys have accommodated again to a normal supply of the hormone, and during the period of accommodation the glomerular filtration goes down to subnormal values and oliguria develops.

It is nearly always possible to overcome the oliguria after operation by means of intravenous injections of hypertonic glucose and isotonic saline solution. A temporary increase of the nonprotein nitrogen content of the serum during the oliguric period quickly vanishes after the urinary output has become normal again. Only in cases of hyperparathyroidism with extensive renal involvement and a high serum inorganic phosphorus before operation, has the removal of the parathyroid adenoma been followed by fatal renal failure.

As far as other complications are concerned, removal of a parathyroid adenoma in a patient with damaged kidneys occasionally has been followed by dangerous acidosis. In three cases of parathyroidectomy acute pancreatitis has been observed to develop after operation.[32]

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Chapter 9

Renal Osteitis Fibrosa

Secondary Hyperplasia of the Parathyroids with or without Osteitis Fibrosa in Chronic Renal Failure

In certain forms of uremia both extensive osteitis fibrosa and generalized hyperplasia of the parathyroids may develop. This syndrome, which carries many different names, occurs only rarely and is practically limited to cases of long-standing uremia with acidosis in children and young adults. The prevalence for the younger age group is clearly expressed in the terms "renal infantilism, renal dwarfism and renal rickets," all of which until recently have been used indiscriminately to designate this disease. The stunting of growth is associated with generalized resorption of bone, which often leads to pain and occasionally causes pathologic fractures. Since it has generally been recognized that the basic bone lesion of these children with uremia consists mainly of osteitis fibrosa, it seems advisable to avoid the designations mentioned above. The terms renal osteodystrophy, renal osteofibrosis or osteonephropathy are more appropriate labels for this disease entity.

The skeletal changes and marked hyperplasia of the parathyroids develop only when the renal insufficiency has lasted for a very long time, i.e., when a marked increase of the blood urea nitrogen, creatinine, uric acid and phosphates, together with a low serum calcium and decreased CO_2-combining power have been present for many years. When the chronic uremia has caused extensive bone lesions, the alkaline phosphatase content of the serum increases, because the lack of skeletal solidity leads to increased activity of the osteoblasts.

The prevalence of the development of renal osteodystrophy in young people can be attributed in part to the fact that the skeleton of children and young adolescents reacts much more intensely to different stimuli than does the bony system of older people. Experimental osteitis fibrosa, induced by such agents as ammonium chloride, lead, or parathyroid extract, is also more easily accomplished in young animals than in older ones. But, in addition, chronic uremia in children and young adults is often caused by congenital anomalies of the kidneys, such as bilateral dilatation of the ureters and the renal pelvis or congenital hypoplasia of the kidneys, usually complicated by chronic interstitial nephritis. When these anomalies lead to chronic uremia, hypertension and changes in the eye grounds are often unimpressive. It follows that in these conditions arteriolar degeneration is less widespread than in chronic glomerulonephritis. This may be a major factor in prolonging the life of this group of young uremia patients. During the long survival period allotted patients with uremia caused by congenital anomalies, the bone lesions and the secondary parathyroid hyperplasia have time to develop.

Contrariwise, in chronic glomerulonephritis and pyelonephritis—the most common causes of uremia in adults—the survival time is limited as soon as a marked increase of blood urea nitrogen and acidosis develops. The old rule still holds true that death can be expected within one year when the blood urea nitrogen rises permanently above 80 mg

per cent in patients with chronic nephritis. Nevertheless, even in older adults uremia due to chronic glomerulonephritis and pyelonephritis, with chronic acidosis and hypocalcemia, may occasionally last long enough to permit the development of renal osteodystrophy and parathyroid hyperplasia.

Hyperplasia of the parathyroids due to renal failure of long duration with acidosis, hyperphosphatemia and hypocalcemia consists mainly of chief cell proliferation. In addition to the chief cells, Castleman and Mallory noted the presence of a greater number of oxyphilic cells than are found in normal parathyroids.[8] A few authors found a moderate increase of water-clear cells in the hyperplastic parathyroids of uremic patients. In these cases there is always a simultaneous proliferation of young chief cells and transitional cells. In short, in contrast to the uniformity of the histologic character of primary generalized hyperplasia of the parathyroids, such uniformity of structure is decidedly lacking in secondary hyperplasia.

BONE LESIONS IN CHRONIC UREMIA

The roentgenologic alterations in the juvenile cases of renal osteodystrophy consist of (1) stunted growth or renal dwarfism, (2) generalized resorption of bone, and (3) changes in the epiphyseal disks—lack of ossification, swelling of the cartilage and deformity of the metaphyses. This delay in enchondral ossification persists in the exceptional patients with juvenile renal osteodystrophy who live to adult age.

Although the closure of the epiphyseal disks is delayed in both renal osteofibrosis and rickets, fundamental differences exist between the radiographic appearance of the abnormal ossification of the epiphyseal disks in these two diseases. In chronic uremia of children and young individuals, the formation of osteoid tissue is much more disorganized than in rickets, causing a much more irregular appearance of the outline of the metaphyseal part of the bone than is commonly observed in rickets. Hence the "woolly" appearance of the metaphysis characteristic of renal osteodystrophy[9,14] does not occur in rickets. The anomalous deposition of osteoid is not generalized one metaphysis may exhibit typical woolly changes while the corresponding metaphysis can remain normal. In rickets, on the other hand, the changes of the epiphyseal disks are always symmetric.

In renal osteodystrophy subperiosteal bone resorption takes place in the metaphysis. This leads to the same characteristic concavity of the cortex of the finger phalanges and resorption of other parts of the skeleton as described in true hyperparathyroidism (PLATE 10a) It is of historic interest that this subperiosteal resorption of bone in chronic uremia, especially in the phalanges, had already been reported in 1928 by Teall,[9] long before attention was drawn to the occurrence of this anomaly in hyperparathyroidism (p 72)

In the long bones of the extremities, subperiosteal resorption, together with the disorganized proliferation of osteoid tissue within the metaphyseal plate, may cause collapse of the metaphysis.[16] In these cases the diaphysis remains intact and impinges upon the crumbled metaphysis, a deformity which is uncommon in rickets, to say the least. (PLATE 12a b) These changes are most clearly seen in the knees, wrists and ankles. The moth-eaten character of the x ray picture of the skull with granular resorption of bone and haziness of both tables that is reminiscent of hyperparathyroidism is rarely observed in rickets.

Finally, in advanced cases of renal osteodystrophy, the widespread osteitis fibrosa leads to a much more marked translucency of the shafts of the bones than is commonly observed in rickets. Another roentgen manifestation of the abnormal calcium and phosphorus metabolism in chronic uremia is the

frequently occurring metastatic calcification. Apart from Mönckeberg's sclerosis of the media of the arteries, calcium deposits may also be found in the subendocardium, the subcutis and especially the synovial layers of the articulations (Plates 12c, 13a). The latter leads to para-articular calcinosis, which often causes redness and swelling of the affected joints. If a juvenile patient with uremia develops "rheumatic fever" or "acute rheumatoid arthritis," the diagnosis of metastatic calcification during renal osteodystrophy with or without secondary hyperplasia of the parathyroids is usually correct.

Exceptional cases of widespread osteitis fibrosa with generalized enlargement of all four parathyroids have also (though rarely) been described in adults with long-standing uremia.[43] Since the epiphyseal disks are closed in adults, the only roentgenologic manifestations of renal osteodystrophy consist of generalized transparency of the skeleton, thickening of the trabeculation of the cancellous bone,[7] subperiosteal bone resorption, especially in the phalanges, and metastatic calcification. Hubbard and Wentworth described such a case as early as 1920, and several others have since been reported.[44,128]

The roentgenologic picture, described in the previous paragraphs, indicates that the term "renal rickets" is a highly inappropriate designation for the lesions of bone and cartilage found in chronic uremia of children and young adolescents. None of the described conditions—the asymmetric character of the epiphyseal disk changes, the woolly appearance of the metaphyseal changes, the collapse of the metaphysis, the subperiosteal bone resorption, the metastatic calcification—occur in true rickets. By way of contrast, the term renal osteofibrosis signifies the basic histologic picture of osteitis fibrosa resulting from prolonged acidosis. It correctly emphasizes the causal relationship of the diseased kidney to the skeleton lesions.

As mentioned before, children suffering from a completely different renal disorder, i.e. tubular dysfunction, leading to Lignac-Fanconi's disease and allied syndromes (p. 43), exhibit typical rachitic changes of the epiphyseal disks (Plate 3c, d). Neither woolly changes of the epiphyseal plate nor subperiosteal bone resorption, etc., is found in tubular dysfunction.[10] Teall recently re-emphasized that cases of tubular dysfunction with genuine rickets must be sharply distinguished from chronic uremia due to glomerular disease with renal osteofibrosis. The true rickety changes of the epiphyseal disks which are found in tubular dysfunctions react favorably upon administration of huge doses of vitamin D. On the other hand, improvement of roentgenographic signs in cases of renal osteofibrosis with woolly changes of the metaphyseal ends cannot be obtained, even if tremendous doses of vitamin D are administered.* Dent has reported that in such cases, treatment of the electrolyte abnormalities may change the character of the bone lesions.[8]

Recently, there has been a revival of the nearly forgotten concept that the bone lesions in true glomerular renal failure might stem from rickets. This revival is based on the results of histologic examination. In microscopic specimens of the skeleton of patients who have succumbed to chronic uremia, a certain degree of impaired calcification of osteoid zones is occasionally encountered amid the typical osteofibrosis.[128] Mitchell, in 1930, explained that the presence of a moderate amount of osteoid zones in this disease is due not to avitaminosis D but rather to the excessive formation of insoluble calcium phosphate in the intestine.[8] In uremia, the diseased kidney does not excrete the phosphates in sufficient quantities. Phosphates accumulate in the blood and are excreted in abnormally large amounts in the intestine. The ensuing calcium phosphate formation interferes with calcium absorption. Hypocalcemia results and insufficient calcium is available for calcification of the bone matrix, hence the moderate amount of osteoid zones

*British experts in this field disagree with this statement.[8a, 128]

around the bone trabeculae which are occasionally found in renal osteofibrosis.

Not everybody agrees with Mitchell's explanation. The authors who still pay attention to the product of Ca x P in the serum emphasize that this product is high in most cases of renal osteodystrophy.[9,11] This, in their opinion, excludes malabsorption of calcium from the intestine. In this connection, it should be noted that after oral administration of phytic acid, so much insoluble calcium phytate is formed in the intestine that no more calcium is excreted in the urine. Nevertheless, calcium and phosphorus of the blood serum—and hence the product of Ca x P also—remain normal. This example demonstrates that the well-known product of Howell and Kramer is not a reliable indicator of the calcium absorption from the gut.

For the time being, Mitchell's explanation of the formation of a moderate amount of osteoid zones in renal osteofibrosis by excessive secretion of phosphate into the intestine still appears to be correct. No justification exists for a revival of the old term of renal rickets. It should be repeated once more that the main histologic feature observed in renal osteodystrophy is general osteitis fibrosa caused by the chronic acidosis the scattered osteoid zones are negligible in quantity and importance.

SECONDARY HYPERPLASIA OF THE PARATHYROIDS "RENAL HYPERPARATHYROIDISM"

The question whether the osteitis fibrosa in chronic uremia develops under influence of hyperfunction of the parathyroids deserves a special discussion.

Erdheim first observed enlargement of the parathyroids in osteomalacia. The same secondary hyperplasia was then found in infantile rickets, avitaminosis D due to chronic fatty diarrhea, in rats kept on a vegetarian diet, and finally in chronic uremia. In none of these conditions except uremia does hyperphosphatemia occur, but hypocalcemia is clearly the common denominator present in all. Nowadays, the long-standing hypocalcemia is generally considered to be responsible for the parathyroid hyperplasia in chronic uremia.

Bergstrand in 1921, was the first to report enlarged parathyroid glands in 10 out of 50 cases of chronic glomerulonephritis.[1] Castleman and Mallory[4] observed enlargement of one or more parathyroid glands in 10 out of 12 cases of chronic glomerulonephritis. In 5 of these cases, the total weight of the 4 parathyroids amounted to 360 630 863 and 864 milligrams, instead of the normal average of 140 milligrams. These clinical observations have been confirmed by ample experimental evidence. After unilateral nephrectomy and removal of part of the other kidney by thermocautery in rats, the resultant nephritic changes in the kidney remnant lead to a hypertrophy of the parathyroids. At the same time, bone changes develop which are comparable to osteitis fibrosa.

It is, of course, tempting to speculate that in uremic patients where both osteitis fibrosa and hyperplasia of the parathyroids coexist, the bone lesions might be caused by hyperfunction of the hyperplastic glands. Many clinicians have succumbed to this temptation, with the result that renal osteodystrophy is commonly considered to be due to "renal hyperparathyroidism." Although it will be difficult to eradicate this popular term, there is still ample room to consider the possibility that bone lesions and hyperplasia of the parathyroids are not interdependent.

There is no definite proof that abnormal amounts of parathyroid hormone are secreted by the hyperplastic parathyroids of patients with renal osteofibrosis. Whereas some authors thought that by the technic of Hamilton and Schwartz an excess of parathyroid hormone could be demonstrated in the blood of patients with renal osteofibrosis, other workers employing the same method obtained negative results.[8] It has since been ascertained

that this biologic assay gives different results in different breeds of rabbits.

Eger's experiments[8] emphasized the importance of the enlarged parathyroids for the causation of the osteitis fibrosa in long standing uremia (p 90) He produced renal degeneration in rats both by uranium and by lead poisoning. This resulted in hyperplasia of the parathyroids and generalized fibrous osteitis. When he removed the parathyroids immediately before the uranium or lead poisoning was initiated, the skeleton remained completely normal. At first view this experiment seems to prove the concept of renal hyperparathyroidism. Other experimenters, however have obtained opposite results. They allowed four months to pass after the parathyroidectomy before starting the uranium or lead intoxication. Under these circumstances, both the uremia and the bone lesions developed exactly in the same way and in the same degree as is the case in non parathyroidectomized animals.[9]

Thus, the experimental evidence remains equivocal. Nevertheless, there are numerous clinical observations of extensive bone lesions in chronic renal failure without enlargement of the parathyroids. All this weakens the hypothesis that in uremia the large parathyroids cause the generalized osteitis fibrosa.

The following data were obtained at the autopsy of four consecutive cases of chronic renal insufficiency with secondary parathyroid hyperplasia

(1) In all four cases the hyperplasia consisted of proliferating chief cells only

(2) In only two cases was extensive osteofibrosis found in the other two the skeleton was practically normal. At most, only occasional thin strands of loose fibrous tissue could be seen, closely adherent to the edges of the bone trabecules.

(3) In all cases the inorganic phosphorus of the serum was constantly high.

(4) Metastatic calcification was found in all four cases. In three, the subcutaneous calcinosis was extensive in two the calcinosis near the joint capsules had led to apparent signs of arthritis.

These four cases confirm the observation that metastatic calcification in uremia is always associated with marked parathyroid hyperplasia. At the same time, often, but not always, extensive osteitis fibrosa is present. No close correlation exists between the histologic changes in the bones and the parathyroid hyperplasia, for in two of four uremic patients in whom large parathyroids were discovered, the bone lesions were negligible. Thus, no irrefutable proof is available for the concept that the renal osteofibrosis is dependent upon the hyperplasia of the parathyroids.

In this connection it must also be stated that neither the clinical nor the histologic picture of renal osteodystrophy seems to indicate the presence of hyperparathyroidism. The delay in the closure of the epiphyseal disks, the woolly character of the metaphysis and the collapse of the metaphyseal part of the diaphysis representing the characteristic signs of renal osteodystrophy have never been observed in children with true hyperparathyroidism. Furthermore in primary hyperparathyroidism with secondary renal failure, hypercalciuria often, but not always, persists. In renal osteodystrophy however the urinary calcium excretion is always less than normal. And, whereas the bone lesions due to true hyperparathyroidism are often remarkably improved under influence of calcium and vitamin D administration, this medication is completely inactive in renal osteitis fibrosa with secondary hyperplasia of the parathyroids (see footnote on p. 89) Thus, other factors apart from parathyroid hyperfunction must necessarily be instrumental in producing the bone lesions in long-standing renal failure.

Since the hypothesis of a secondary renal hyperparathyroidism is far from proven, it seems wise to consider whether the changes in the electrolyte metabolism that occur in uremia could be responsible for the causation of both bone changes and parathyroid hyperplasia. Accumulation of phosphates, sulphates and organic acids in the blood is a constant occurrence in uremia from which acidosis ultimately must ensue. There is ample experimental evidence to show that acidosis causes

widespread osteitis fibrosa which histologically cannot be distinguished from the bone lesions found in hyperparathyroidism. This is only another example of the well-known observation that osteitis fibrosa always develops when rapid absorption of bone takes place, regardless of the cause of the bone resorption.

The parathyroid hyperplasia is also due to the change of the inorganic metabolism in uremia. As explained by Mitchell, the intestine becomes the main path along which the phosphates are eliminated. The formation of large amounts of almost insoluble calcium phosphates impairs the absorption of calcium from the intestine, and results in hypocalcemia and hypocalciuria. The long, drawn out hypocalcemia causes the secondary hyperplasia of the parathyroids.

It thus seems possible—indeed, probable—that osteitis fibrosa in long-standing uremia is not caused by the simultaneously present hyperplasia of the parathyroids. Both anomalies—the bone lesions and the increase in the size of the parathyroids—could well develop independently under the influence of two different uremic metabolic anomalies acidosis causing the bone lesions and hypocalcemia causing the parathyroid hyperplasia.

In many cases the differentiation between chronic uremia with extensive osteitis fibrosa and secondary parathyroid hyperplasia on the one hand, and true hyperparathyroidism with ensuing uremia on the other may be very difficult. The following points may be of help for the differential diagnosis.

Primary hyperparathyroidism with secondary uremia due to nephrocalcinosis should be diagnosed in the presence of these conditions

1 Marked hypercalcemia and hypercalciuria.

2 One or more normal parathyroids, in addition to one or more parathyroid adenomas.

3 Generalized hyperplasia of parathyroids due to proliferation of large water-clear cells.

4 Normally closed epiphyseal disks in young persons.

5 Recalcification of the skeleton in general, and of osteoclastomas in particular (PLATES 7a 8a), if—erroneously—calcium salts and vitamin D have been given.

6 A total weight of all parathyroids above 20 grams.

7 Presence of giant-cell tumors.

Osteoclastomas do *not* occur in patients with uremia and secondary hyperplasia of the parathyroids. However, in renal osteofibrosis the development of bone cysts, though rare, has been observed. Fundamental differences exist between these two bone lesions. Osteoclastomas are the result of the proliferation of the osteoclasts, often under the influence of the secretion of an excess of parathyroid hormone. Bone cysts occur in weakened bone as the result of traumatic influences, irrespective of the cause of the bone disease. Cysts are therefore also observed in uremic osteitis fibrosa.

Secondary hyperplasia of parathyroids in chronic uremia should be diagnosed in the presence of the following conditions

1 Delayed closure of woolly epiphyseal disks with collapse of metaphyses.

2 Failure of normal growth dwarfism, infantilism.

3 The presence of congenital renal anomalies, especially in children favors—but doesn t prove—the diagnosis of primary renal insufficiency with secondary hyperplasia of the parathyroids. It must be stressed that several cases of primary hyperparathyroidism in patients with horseshoe kidneys and polycystic kidneys have been reported. Recently we saw four typical parathyroid adenomas in a patient with a congenital dilatation of one ureter and hypoplasia of the other kidney

In adults, the diagnosis of primary hyperparathyroidism is always more probable than that of renal osteopathy The reverse is true in children, because primary hyperparathyroidism is rare in childhood.[2]

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Primary hyperparathyroidism with secondary uremia due to nephrocalcinosis should be diagnosed in the presence of these conditions:

1. Marked hypercalcemia and hypercalcuria.

2. One or more normal parathyroids, in addition to one or more parathyroid adenomas.

3. Generalized hyperplasia of parathyroids due to proliferation of large water-clear cells.

4. Normally closed epiphyseal [...] young persons.

5. Reossification of the skeleton [...]eral, and of osteoclastomas in p[...] (PLATES 7a, 8a), if—erroneously—[...] salts and vitamin D have been given.

6. A total weight of all parathyro[...] 20 grams.

7. Presence of giant-cell tumors.

Osteoclastomas do not occur in [...] with uremia and secondary hyperp[...] the parathyroids. However, in ren[...] fibrosa the development of bone cysts[...] rare, has been observed. Fundamenta[...]ences exist between these two bone[...] Osteoclastomas are the result of the [...]ation of the osteoclasts, often under [...]fluence of the secretion of an excess [...]thyroid hormone. Bone cysts occur i[...]ened bone as the result of traumat[...]ences, irrespective of the cause of t[...] disease. Cysts are therefore also obs[...] uremic osteitis fibrosa.

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Chapter 10

Metastatic Calcification after Medical Treatment of Peptic Ulcer Burnett's Syndrome

Clinical experiences in hyperparathyroidism clearly demonstrate that dietary influences should not be underestimated in the causation of metastatic calcification. As a matter of fact, the administration of large amounts of calcium, phosphate and vitamin D to patients with hyperparathyroidism should be avoided. Although in the course of this treatment the subjective complaints of these patients improve and recalcification can be obtained (Plates 7a 8a), dangerous nephrocalcinosis develops much more rapidly than when such patients are kept on a low calcium diet.

For many years, excessive ingestion of alkali and milk for the treatment of ulcer patients with Sippy diet and powders has been known to cause acute alkalosis, with severe polydipsia, polyuria and mental confusion.[7] In such cases, the CO_2-combining power of the serum rises to very high levels, and more or less pronounced hypercalcemia and retention of water are usually present. When the Sippy diet and powders are stopped, these signs disappear in a few days.

Burnett and associates have emphasized that administration of large quantities of both milk and alkali over many years may lead to metastatic calcification of subcutaneous tissue and visceral organs, especially of the kidneys.[8] Under these circumstances, changes of calcium and phosphorus content of the serum and urine ensue, which could possibly be confused with hyperparathyroidism. There is experimental support for the theory that these anomalies may be part of a general metabolic pattern.

Among the metabolic changes which may develop, the markedly increased citric acid excretion in humans on a high alkali intake must be mentioned.[18] This has thrown light on the older experiments of A. Polak.[19] The latter in a very thorough investigation, showed that addition of calcium carbonate to a fixed diet leads to the formation of kidney and bladder stones in young male rats. These concrements were identified as calcium citrate stones.[19] This stone formation was obtained by the addition of 3 per cent calcium carbonate to the diet, and it must have been closely dependent on the resulting alkalosis. No calculosis appeared when equivalent quantities of potassium phosphate or calcium chloride were substituted for the calcium carbonate. Almost without exception, in all calcium carbonate experiments the urine was found to have a relatively high pH, the range varying between 7 1 and 8.5. The rats, kept on a calcium chloride diet, excreted urine with a pH in the range of 5 6 to 6.5. In Polak's experiments the influence of the calcium carbonate ingestion on the citric acid excretion was not directly checked. Nevertheless, it would seem that the formation of calcium citrate stones in the kidneys and bladders of these animals was caused (1) by the large amounts of calcium ingested and (2) by the excretion of citrate caused by chronic alkalosis. It might be pertinent to mention the experiments of Butler,[4] who found that mice which were given an alkaline diet for eight to fourteen days developed calcium deposits in the lungs, stomach, and kidneys. In these experiments, the pH of the urine was not recorded.

It thus becomes readily apparent that the

sequelae of a Sippy diet continued for several years are not alone caused by the calcium carbonate and calcium phosphate accumulated in the blood. The important role of chronic alkalosis in the causation of metastatic calcification in patients who for many years have been following a Sippy diet and alkali medication, should not be underrated.

Burnett et al. have described the hypercalcemia with hypocalciuria, often accompanied by mild alkalosis and metastatic calcification, that develop in such patients. Hyperphosphatemia is commonly a part of this syndrome, due in part to the uremia and in part to the high phosphate content of the milk. This indicates that not only the calcium but also the phosphorus of the milk must play a role in the production of this syndrome. Ultimately marked renal insufficiency with azotemia ensues; in this stage, the alkalosis is replaced by acidosis. Amorphous calcium masses are deposited in the subcutaneous tissue, mainly in the neighborhood of the articulations, in the synovial membranes and even in tendons. Often the calcium deposition also involves visceral organs, especially the kidneys, blood vessels, dura mater falx, diaphragm, and bronchial tree.[11] The presence of band-shaped keratitis or keratopathy can frequently be elicited by slit lamp examination. Granular subepithelial deposits running concentrically with the limbus are found in the cornea. Small calcium particles may be present in the conjunctiva.

The urinary calcium excretion is nearly always within normal limits and is often even low. The alkaline phosphatase of the serum is normal; anemia is usually present. If this syndrome is discovered in an early stage the onset of uremia may be prevented by the cessation of the milk and alkali ingestion. However at least one patient with Burnett's syndrome died one year after milk and alkali administration had been eliminated. During this period, a gradual resorption of the subcutaneous calcium deposits near the wrist, shoulder and scapula took place. The blood chemistry did not change. Evidently the kidney damage due to nephrocalcinosis had been irreversible.

The differentiation of this condition from hyperparathyroidism is often facilitated by the absence of generalized osteitis fibrosa, giant cell tumors and other skeletal anomalies, hypophosphatemia and hypercalciuria. In Burnett's syndrome the subcutaneous calcium deposits are much more extensive than in hyperparathyroidism. After withdrawal of milk and Sippy powders, the serum calcium and phosphate return to normal, whereas in hyperparathyroidism, the hypercalcemia is not easily improved by such dietary changes. When calcium metastases develop in patients with long standing uremia, the serum calcium is nearly always lower than normal, the hyperphosphatemia is excessive (p. 89), and dietary measures have little or no influence on the calcium and phosphorus contents of the serum (see table 2). Nevertheless, differential diagnostic difficulties occasionally arise. Schneider reported one patient evidently suffering from Burnett's syndrome who at least on one occasion had hypercalciuria during a period of low calcium diet.[18] On the other hand, when a patient with hyperparathyroidism develops marked renal insufficiency—or suffers from superimposed avitaminosis D—hypercalciuria may be replaced by hypocalciuria. Carpenter and Pautler observed a patient who manifested many of the signs of the Burnett syndrome. However, there was no history of excessive intake of alkali. At autopsy, the presence of a parathyroid adenoma was elicited which had not been found at a previous exploratory operation of the neck.[4] Other comparable observations have recently been published.[1]

It is thus imperative that the diagnosis of Burnett's syndrome not be made unless there has been a high alkali intake for many years, with or without a high calcium intake. Prompt improvement should be obtained by cessation of the milk and alkali treatment. Finally marked resorption of bone and especially the presence of osteoclastomas militate against the diagnosis of Burnett's syndrome.

TABLE 2

	Hyperparathyroidism	*Chronic Uremia*	*Long-standing Milk Diet and Alkali Administration*
Serum Ca	Increased	Decreased	Increased
Serum P	Decreased	Increased	Increased
Calciuria	Increased	Decreased	Decreased
Nephrocalcinosis	Frequent	Rare	Very Frequent
Subcutaneous calcinosis	Rare	Frequent	Very Frequent
Uremia	Frequent	Constant	Moderate if present
Influence of restriction of calcium and phosphorus intake	No	No	Yes
Roentgenological survey of skeleton	Generalized osteitis fibrosa	Renal Osteofibrosis	Normal
History of intake of milk and alkali	No	No	Yes

We reported two additional cases of metastatic calcification in ulcer patients. In both cases a large amount of a proprietary alkali preparation (Alka-Seltzer) had been ingested.[14] In one instance the additional daily ingestion of calcium was very high, while in the other the calcium intake was actually lower than the recommended daily requirement. The latter case indicates that alkalosis alone, without a high ingestion of calcium, may lead to metastatic calcification and hypercalcemia.

The first patient, a man of 62 years, had treated his peptic ulcer for ten years by drinking large quantities of milk, about three quarts a day. Concomitantly he was taking Alka-Seltzer in such large amounts that he bought the latter preparation wholesale.

On admission, he was frankly uremic with a blood pressure of 115/80. There was a rubbery non tender mass, 8x8x3 centimeters, in the left infraclavicular fossa, another 1.5 centimeters mass in the pulp of the distal phalanx of the left index finger and a third one over the right olecranon process. Calcific deposits were also found in the conjunctivae. The urine showed a specific gravity varying between 1.010 and 1.016, the reaction varying between acid and alkaline. Albumin was 3 to 4 plus, there were rare red blood cells, and occasionally many white blood cells. Qualitative reaction for calcium (Sulkowitch method) was negative. Moderate anemia with hemoglobin of 10.1 Gm. per cent was present. Blood chemistry showed an increase of blood urea nitrogen to 53 mg. per cent, frank acidosis, CO_2-combining power 33 volume per cent, markedly increased creatinine, 11.6 mg. per cent and inorganic phosphate, 11 mg. per cent. Other figures obtained were uric acid, 5.3 mg. per cent, calcium, 9.3 mg. per cent, alkaline phosphatase, 12 King Armstrong units, sodium, 128 mEq., potassium, 3.9 mEq., serum albumin, 2.1 Gm. per cent, serum globulin, 2.9 Gm. per cent. Widespread nephrocalcinosis was found on the roentgenograms. The soft tissues about the shoulders (PLATE 13c, d), elbows and hips contained large amorphous calcific deposits.

After his third hospital day, the patient

was noted to be anuric. He remained thus until his death on the tenth hospital day. Patient's blood urea nitrogen rose gradually to 120 mg. per cent while his serum chloride fell to 480 mg. per cent. On his last three hospital days, he had epileptiform seizures. A few weeks before admission his physicians had forbidden him to drink milk, because it was evident that milk was one of the causes contributing to the uremia. This, in connection with his uremia, may well have been the reason the calcium of the serum had come down to normal values on admission.

The second patient was a 65 year old white female who had treated her duodenal ulcer for fifteen years with a meat free, alkaline ash–type diet. For the past eight years she had been taking an average of three tablets of Alka-Seltzer daily, which she found to be quite effective in relieving her ulcer pains.

In August, 1952, the serum calcium was 12.05 mg. per cent, the serum phosphorus, 5.9 mg. per cent. In October, 1952, x rays revealed metastatic calcification involving both kidneys, the ascending and descending aorta and its branches, and both femoral arteries. There were also subcutaneous calcifications superior to both greater trochanters, in areas superior to both scapulae, and in the soft tissues of the neck. Laboratory findings were then: serum calcium, 11.5 mg. per cent; serum phosphorus, 6.4 mg. per cent; serum albumin, 5.2 mg. per cent; serum globulin, 2.8 Gm. per cent; blood urea nitrogen, 43.4 mg. per cent.

In November, 1952, incipient band-shaped keratitis of both eyes (calcifications of Bowen's membrane) was found. The bulbar conjunctivae in the inner palpebral area showed peculiar opaque plaques and flecks, some of which appeared continuous with corneal opacification. Large opacities were present in the central area of each tympanic membrane, white and irregular in outline.

Hemoglobin was 12.5 grams. Urinalysis showed specific gravity 1.010; pH, 7.0; protein, +1; Sulkowitch, +1. Urea clearance was 4.8 cc. (standard, 41.0 cc.). During the Kepler Power water test, the specific gravity remained 1.010 with half hour volumes varying from 2 to 70 cc. P.S.P.—25 per cent excreted after 120 minutes. Serum calcium was 12.0 mg. per cent. On a low calcium intake of 118 milligrams per 24 hours, the urinary calcium excretion was 202 milligrams per 24 hours with a 1417 cc. output, and 148 milligrams per 24 hours with a 680 cc. output. X ray of the upper gastro-intestinal tract revealed a markedly deformed and narrowed duodenal cap, probably secondary to an old duodenal ulcer. No crater was identified at this time.

The average calcium intake in food and medicine during the past five to ten years had ranged around approximately 800 milligrams of calcium per 24 hours.

It is interesting to note that Becker et al. found an incidence of 36 per cent of renal parenchymal calcinosis in a review of 99 autopsy cases of chronic active or healed duodenal ulcer.[8] Sixty-eight per cent of these individuals had a history of a high intake of absorbable alkalies. These authors suggested that the renal parenchymal calcification was possibly due to both the large amounts of calcium in the diet and the transient asymptomatic episodes of alkalosis. In none of these cases was the involvement severe enough to cause renal failure.

Our first patient with metastatic calcification caused by a dietary etiology fits quite well with the published cases of Burnett's syndrome.[4,9,11] The second seems to be unique in that the calcium intake was below recommended daily requirements, thus leaving the alkaline ash diet and excess alkali ingestion as the only observable dietary deviations. This observation seems to indicate that the excess of alkalinizing agents could well be the more important factor in the growing series of cases of pathologic calcification due to dietary causes.

The question has been raised whether metastatic calcification develops especially in ulcer patients whose kidneys had been dam-

aged before the milk diet and alkali administration had been started. No pre-existing renal disease was elicited in the history of our two patients. However the presence of four plus and one plus albuminuria and the low specific gravity raised the question of the possibility of pre-existing pyelonephritis.

In this connection, the interesting observations of Swyer[15] and his associates on hypercalcemia in patients with osteolytic metastases after androgen therapy should be mentioned. At autopsy such patients always show signs of pre-existing disease. In the same way it seems possible the calcinosis, hypercalcemia, and uremia are more likely to develop when patients treated with alkalies and/or a Sippy regime have pre-existing renal disease.

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Chapter 11

Boeck's Sarcoidosis Nephrocalcinosis and Skeletal Involvement

IN 1899, CESAR BOECK DESCRIBED A DISEASE in which small reddish papules developed within the skin.[2] With glass pressure a brownish lesion could be visualized which at microscopic examination proved to have a tuberculoid structure. The initially bright red papules later became yellowish or brown. Sometimes large numbers of these subcutaneous papules accumulated, resulting in thickening and reddish-blue discoloration of the overlying skin. The latter modality of sarcoidosis had already been described in 1889 by Besnier under the name lupus pernio, or chillblain lupus.

Other names used in place of Boeck's sarcoids are benign miliary lupoid, Mortimer's malady (Hutchison) uveo-parotid fever (Heerfordt) lymphogranuloma benignum (Schaumann), osteitis tuberculosa multiplex cystoides (Jüngling), and Mylius-Schürmann's disease.

There has been great confusion about the nature of Boeck's sarcoids because, microscopically these pseudotubercles are somewhat similar to tuberculous lesions.[17] In the center of the sarcoids one or more Langhans giant cells surrounded by several layers of epithelioid cells are found. The outer layer is formed by many layers of lymphocytes. Laminated inclusions and asteroid bodies are often seen in the giant cells. These inclusions stain deeply blue with hematoxylin. Remarkable as the asteroid bodies are, they are not completely pathognomonic of Boeck's sarcoids. Sarcoids can be differentiated from true tubercules by the absence of either caseation or calcification. In addition, the sarcoids are sharply delineated from the adjoining tissue due to the absence of collagen changes in blood vessels. This is in marked contrast to the frequent arteritis which abounds near tuberculous lesions. In sarcoids, acid fast bacilli cannot be found by microscopic examination, culture or animal inoculation. Moreover, an antigen can be prepared from sarcoid tissue which can be used for a specific skin reaction. For this Nickerson Kveim reaction an emulsion of a lymph node, affected by sarcoidosis, is injected subcutaneously The area of injection must be biopsied six weeks after the injection, and in the event the patient suffered from Boeck's sarcoidosis, a typical sarcoid is found at the site of injection.[16] The tuberculin reaction of these patients is usually negative. Sarcoidosis has repeatedly been observed in siblings, and familial factors may well play a role in the development of this disease.[18]

The lesions of sarcoidosis are often present at the same time in many different organs lungs, lymph nodes, kidneys, eyes, liver, spleen, bones, parotis, etc. This is another contrast with tuberculosis. When tuberculosis is present in several organs at the same time, the outlook is very poor whereas the prognosis of widespread sarcoidosis is usually favorable.

It is therefore, generally agreed that Boeck's sarcoids are not tuberculous in nature. On the other hand, patients with Boeck's sarcoids are very susceptible to tuberculous infections in the terminal stage of sarcoidosis tuberculosis frequently develops. In this respect, Boeck's sarcoids is similar to diabetes, Hodgkin's disease and other diseases where tuberculosis also often develops as a terminal

complication. The fact that patients with sarcoidosis often die from a terminal tuberculous infection is therefore no justification for the concept that Boeck's sarcoids are closely connected with tuberculosis.

Boeck had already reported that the sarcoid lesions he described were not limited to the subcutaneous tissue, but were sometimes present in other organs too. Schaumann in 1914 strongly advocated that Boeck's sarcoidosis represents a generalized disease, presenting itself in the form of many different clinical syndromes.

The diagnostic importance of the visceral invasion of Boeck's sarcoids was readily understood when it became evident that so-called "*chronic or healed miliary tuberculosis*" was due to a submiliary dissemination of sarcoids through the lungs. Another clinical problem was solved by the realization that sarcoidosis was the cause of large bilateral hilar lymph nodes in patients with a negative tuberculin reaction.

The skeletal lesions stemming from Boeck's sarcoids were first described in 1920 by Jüngling as "osteitis tuberculosa cystoides." In his patients, well circumscribed osteolytic cystlike lesions were present in the phalanges of the hands and feet. The cystic lesions were filled with "tubercles" and granulation tissue. The name osteitis tuberculosa cystoides later had to be changed when it became evident that the tubercles found in the phalanges of this patient were not caused by tubercle bacilli, but were identical to Boeck's sarcoids. The small round osteolytic lesions are located in the cancellous bone, mainly in the distal parts of the middle phalanges (PLATE 13*b*) Less frequently are these lesions found in the proximal phalanges, the metacarpals and the metatarsals.[9] The cystic lesions may coalesce to larger osteolytic areas, which then destroy a considerable part of a phalanx. The spread of the tubercle like structures through the bone is always much *more* extensive than can be visualized on the roentgenograms. Sometimes at biopsy the entire spongious bone of the phalanx may be *involved*, although no roentgenologic lesions are found. Diffuse miliary dissemination through the cancellous bone may lead to the formation of a "*stippled pattern*," where tiny osteolytic dots are present against a background of normal bone.[9] When these small groups of sarcoids coalesce, so-called "lattice" structures may ultimately result.[17]

It should be noted that in all the different manifestations of the proliferation of Boeck's sarcoids in the bones, thickening of the subperiosteal tissue is always absent.

In most cases where phalangeal bone lesions are present, the overlying skin presents the typical picture of chilblain lupus. The skin is thickened and shows a reddish and cyanotic *discoloration*. *Glass* pressure reveals the presence of multiple small brownish sarcoids. The reverse is also true when lupus pernio or chilblain lupus is present on the fingers, cystlike phalangeal lesions will nearly always be found. Since chilblain lupus—like uncomplicated chilblains and lupus vulgaris—has always been rare in the United States, phalangeal lesions due to sarcoidosis are much less frequent here than in the old country Nevertheless, in every patient with Boeck's sarcoidosis roentgen photos of the skeleton of hand and feet are made. It can be safely estimated that in at least 99 per cent of such patients who do not suffer simultaneously from chilblain lupus, no bone lesions will be found. Only exceptionally have phalangeal cystlike lesions been described in patients with Boeck's sarcoidosis who had no lupus pernio of the fingers.

In contrast to this statement, certain reports indicate that bone lesions occur in 15 per cent of the cases of Boeck's sarcoids. In King's large series, 42 cases of bone lesions were observed in 279 patients with sarcoidosis.[10] Most of the statistics which report such a *high incidence of bone lesions in* Boeck's sarcoidosis have been compiled in departments of dermatology where patients with Boeck's sarcoidosis are admitted *because* they have skin lesions. It can be understood that in such selected groups of cases both skin

lesions and skeletal lesions are frequent. The greater majority of patients with Boeck's sarcoids are admitted to a medical department, complaining of lymph node swelling or fever of unknown origin or remarkable pulmonary lesions or eye lesions, but usually without skin lesions. In this group of patients the frequency of skeletal lesions is decidedly very much smaller than 15 per cent.

In comparison with the phalangeal lesions, other bone lesions due to Boeck's sarcoids are rare.[5,13] In general, the smaller bones are much more frequently affected than the long bones, perhaps because the skin over small bones is more liable to be affected by lupus pernio than the skin covering the long bones. When chillblain lupus is present in face and nose, the underlying bone is usually diseased, and destruction of the nasal bones is frequently observed. In the larger bones the sarcoid lesions usually consist of rather extensive osteolytic areas which could easily be confused with other diseases. Hypercalcemia and hypercalciuria are encountered in 20 to 45 per cent of the patients with Boeck's sarcoids. Increase of the alkaline phosphatase of the serum is also found, but less frequently.[6,13] In the active state hyperglobulinemia commonly occurs, but the increase of the serum globulin cannot be held responsible for the hypercalcemia.[11] The serum phosphorus, which may be high due to nephrocalcinosis and ensuing renal damage, is however usually normal.

The cause of the hypercalcemia in Boeck's sarcoids is not clear. Originally it was believed that the frequent invasion of the cancellous bone by sarcoidosis might be the cause of the hypercalcemia.[6] However no correlation exists between the extent of the bone lesions and the intensity of the hypercalcemia. The interesting experiments of Albright et al.[7,8] seem to point to the possibility that in the intermediary metabolism of patients with Boeck's sarcoids, vitamin D–like substances are formed which lead to increased intestinal absorption of calcium, hypercalcemia and hypercalciuria. The increased absorption of calcium from the intestine was proven by balance studies. For instance, in one patient with Boeck's sarcoids and hypercalcemia kept on a low calcium diet (which in normal individuals would lead to a fecal excretion of 200 milligrams of calcium), only 8 milligrams were eliminated daily in the stools. Moreover, sarcoidosis patients are hypersensitive to vitamin D, relatively small amounts of this vitamin cause hypercalcemia and hypercalciuria.

Hypervitaminosis D, although characterized by hypercalcemia and hypercalciuria, does not lead to an increase of the alkaline phosphatase of the serum. The latter anomaly, which is rather frequently found in Boeck's sarcoidosis, must therefore be explained differently. In this respect, the nearly constantly present dissemination of Boeck's sarcoids in the liver may be of importance. Such dissemination must lead to a proliferation of cholangioles which, in its turn, may cause an increase of the alkaline phosphatase of the serum.

The hypercalciuria of patients with Boeck's sarcoids may cause the formation of renal stones and nephrocalcinosis, sometimes of soft tissue calcifications. Van Creveld[10] reported that in five of six children with sarcoidosis, hypercalcemia was present, nephrolithiasis was found in two and calcium metastases in the soft tissues were found in one. Longcope and Freiman[11] observed four cases of Boeck's sarcoids with nephrolithiasis. Davidson and associates[4] observed seven cases with hypercalcemia and nephrolithiasis, two of which had soft tissue calcifications, two others, nephrolithiasis. Only one of these seven patients had discrete bone involvement. The calcium metastases were localized around the joints. The very severe arteriosclerosis in two of their patients, 32 and 38 years old, respectively, may well have been another manifestation of metastatic calcification.

The roentgenologic aspect of the nephrocalcinosis is the same as is found in hyperparathyroidism. Again the calcifications are present in pelvis, calyces and medullary

viously the patient's identical twin brother had been operated on for a parathyroid adenoma.

It must therefore be repeated that the finding of Boeck's sarcoids at biopsy does not exclude the presence of another completely independent ailment.

Specific treatment of Boeck's sarcoids is nonexistent. It is true that the lesions rapidly disappear under corticosteroid treatment,[18] but unfortunately the lesions recur soon after cessation of the medication. Cortisone decreases the excessive absorption of calcium from the gut that exists in Boeck's sarcoids and brings the hypercalcemia and hypercalciuria of these patients back to normal levels.[8,14] As far as is known, hypercalcemia and hypercalciuria do not readily recur after the cortisone treatment has been stopped. A comparable therapeutic result can be obtained by the oral administration of phytic acid or sodium phytate.[8] This leads to the formation of insoluble calcium phytate in the intestine and restricts the intestinal calcium absorption to such a degree that only traces of calcium appear in the urine.

Sodium phytate is administered in a 15 percent solution which contains about 80 per cent pure sodium phytate. Daily, 8.8 grams of sodium phytate are given in divided doses, i.e., about 4 to 5 tablespoons of the 15 percent solution diluted in a glass of water. The only side action of such doses of sodium phytate is painless diarrhea, which disappears readily after the medication is stopped.

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Chapter 12

Hypoparathyroidism and Pseudohypoparathyroidism

HYPOPARATHYROIDISM

HYPOFUNCTION OF THE PARATHYROID glands results when these tiny structures are damaged during a thyroidectomy In other cases the condition is congenital and is designated idiopathic hypoparathyroidism.

Formerly, the vast majority of cases of hypoparathyroidism were the aftermath of injury to or removal of the parathyroid glands during thyroid surgery Partly due to careful identification of the parathyroid glands during the operation, but mainly due to the replacement of the majority of thyroidectomies by modern medical therapy of Graves's disease, the postoperative type of hypoparathyroidism has fortunately become uncommon. When the glands have been only damaged, but not removed, regeneration may occur The symptoms of hypoparathyroidism then disappear spontaneously after several months.

In the postoperative type of hypoparathyroidism, damage to the parathyroids is manifested by degeneration or fibrosis of the glands, whereas in the idiopathic variety glandular tissue is replaced by fat, with a diminution in the number of remaining epithelial cells.

As mentioned before, parathyroid hormone increases phosphate excretion in the urine by inhibiting the reabsorption of phosphates in the tubules of the kidney In addition, it increases osteoclastic resorption of bone and enhances calcium absorption from the intestine (p 61) Thus, in the presence of inadequate function of the parathyroid glands, the excretion of phosphorus in the urine is decreased and the serum phosphorus level rises. At the same time, the stimulation of the osteoclastic activity of bone by parathyroid hormone dwindles and calcium ceases to be resorbed from bone at a normal rate. Finally unless extra vitamin D is administered, the intestinal absorption of calcium falls below the normal levels. Thus, in hypoparathyroidism, hypocalcemia, hyperphosphatemia, hypocalciuria and hypophosphaturia are constant findings. As soon as the serum calcium has fallen below the level of 8 milligrams per 100 cc., the urinary calcium excretion sinks to such low levels that, after addition of the Sulkowitch reagent to the urine, only a faint precipitate is formed.

The decrease in the ionized serum calcium causes an increased neuromuscular excitability When the serum calcium falls below 6 milligrams per cent, tetany results. In this condition the serum phosphorus is always above 6 and may even reach 12 milligrams per cent.

In tetany the neuromuscular excitability is so much increased that a characteristic syndrome develops. Insidious paresthesias, numbness and tingling of the extremities, muscular cramps, a feeling of stiffness in hands, feet and lips, twitching of face and eyelids can be observed, finally culminating in overt carpopedal spasms and laryngeal stridor Generalized epileptiform convulsions may even occur in severe cases. Carpopedal spasm leads to the obstetrical hand, a characteristic position, consisting of flexion at the elbow wrist and metacarpophalangeal joints, ex

tension at the interphalangeal joints, and adduction of the wrist and thumb Comparable changes are seen in the feet. Laryngeal stridor may be erroneously diagnosed as "croup" or bronchial asthma and if not properly treated, may lead to asphyxia. The convulsions of tetany are most frequently mistaken and treated for epilepsy, especially because the electroencephalographic changes in both conditions are similar In addition, in tetany, incontinence of urine and drowsiness after the attack have been observed However, the tetany attacks are usually not preceded by an aura. Apart from the immediate hazards of tetany younger patients with long standing hypoparathyroidism frequently show signs of mental retardation.

Latent tetany may present only as grimacing, awkwardness, tremor, stumbling, and muscular rigidity Following excitement or emotional disturbance, latent tetany may change to typical attacks of tetany This transition from latent to manifest tetany especially occurs during periods of increased physiologic demand for calcium, as in pregnancy or in the postpartum period. The onset of tetany in some cases has followed an acute viral disease, e.g., measles and influenza.

A positive Trousseau sign is diagnostic of tetany This consists of the induction of a carpal spasm when the venous return from the arm is occluded with a tourniquet or blood pressure cuff for three minutes. Chvostek's sign is a twitching of the muscles of the lip or about the eye, when the facial nerve is tapped in its superficial portion just anterior to the ear Twitching after tapping of any other part of the cheek only means increased sensitivity of the muscle to mechanical stimulation. The latter should not be confused with a true Chvostek sign, which is caused by an increased sensitivity of the motor nerve to mechanical stimulation. Since Chvostek's sign can be elicited in many normal individuals, its presence is not pathognomonic of hypocalcemia. However in the absence of Chvostek's sign the presence of hypocalcemia is improbable. If the serum level of ionized calcium is at threshhold values it may be necessary to demonstrate abnormal neuromuscular excitability by electrical stimulation

Since tetany is merely a manifestation of a diminution of the ionized calcium of the serum, its occurrence is also common in other hypocalcemic or even normocalcemic conditions, which must be carefully distinguished from hypoparathyroidism. In general, these fall into three groups

1 States of alkalosis in which the total serum calcium levels are usually normal, but the diffusable or ionized calcium fraction is diminished. This is seen during hyperventilation following loss of gastric hydrochloric acid as a result of persistent vomiting, after ingestion of large amounts of alkali (as in the treatment of peptic ulcer) and, finally, in the course of gastrointestinal infections. Serum phosphorus and phosphatase levels are normal in such cases. The urine is alkaline and contains normal amounts of calcium.

2. States of deprivation of both calcium and vitamin D such as occur in starvation, pregnancy and lactation, rickets, osteomalacia and steatorrhea. Fatty diarrhea often leads to failure of absorption of fat soluble vitamin D and to excessive loss of calcium soaps (p 40) In all these conditions the hypocalcemia is accompanied by a low or normal serum phosphorus level.

3 Renal insufficiency In states of chronic azotemia, hyperphosphatemia combined with depression of the serum calcium level is a constant sign. It may be that in some such cases the tendency toward tetany is counteracted by the associated acidosis, which tends to increase the ionized calcium available in the serum.

In an analysis of 52 cases of idiopathic hypoparathyroidism from the literature, Steinberg and Waldron[14] defined the criteria for the diagnosis of idiopathic hypofunction of the parathyroid glands as follows

1 A low serum calcium level.
2. A high serum inorganic phosphorus level above 6 milligrams per 100 cc. in adults

and above 7 milligrams in children under 16 years of age.

3 The absence of renal insufficiency

4 The absence of rickets or osteomalacia at roentgenologic examination.

5 The exclusion of chronic diarrhea and alkalosis due to persistent vomiting or hyperventilation.

Forbes, who alone observed 7 patients with idiopathic hypoparathyroidism, adds another criterion.[9] Upon administration of parathyroid hormone, serum calcium and urinary phosphorus should increase.

Heredity is hardly ever a factor Very rarely has the disease been observed in siblings. In a few exceptional cases, the mothers of children with idiopathic hypoparathyroidism had previously suffered from hyperparathyroidism.[5,10]

Frequently, idiopathic hypoparathyroidism is associated with ectodermal changes, such as blepharitis with ensuing photophobia. Cataracts occur in about half the cases, and changes of skin, nails or hair occur in more than one fourth of the cases. The cataracts, which are assumed to be due to local deposition of calcium, are also encountered in other hypocalcemic conditions with a completely different etiology, e.g., sprue. In such circumstances the formation of cataracts can be prevented by the serum calcium being raised to a normal level. The coarse, dry and scaly skin and the thin, sparse hair are reminiscent of hypothyroidism. Complete alopecia has also been observed, and in some cases the eyebrows and the body hair had completely disappeared.

The deformed, ridged and brittle nails resemble the lesions found in moniliasis. In this connection it may be of some importance that 10 per cent of the patients with idiopathic hypoparathyroidism actually suffer from concomitant monilia infections. In hypoparathyroidism, the nails of fingers and toes are often completely lost.

Adrenocortical insufficiency has repeatedly been observed, associated with hypoparathyroidism,[11] and was present in two of the seven patients of Forbes.[9]

The poor dentition is of special interest. If the hypoparathyroid state develops before the teeth are completely formed, aplasia or hypoplasia of the enamel of the teeth results (Plate 15*d*) Thus, the onset of the process may be dated from the time the changes of the teeth started.

Papilledema was found in 7 of Sternberg's and Waldron's 52 cases 3 of their patients had increased cerebrospinal fluid pressure. Calcification of the basal ganglia of the brain in hypoparathyroidism is often used as additional evidence for local calcium deposition (Plate 14*c*) In 7 of the 52 cases analyzed by Sternberg, and in one of Forbes's patients, such calcification was demonstrated roentgenologically Mental retardation was present in 4 of Sternberg's cases, generalized physical retardation, in 3 Even psychotic behavior has been observed. One patient had polydactylism.

Electroencephalographic abnormalities are common, though not distinctive. The abnormality consists of a diffuse increased activity similar to that seen in the grand mal variety of epilepsy Electrocardiographic abnormalities are limited to prolongation of the Q-T interval due to the presence of hypocalcemia.

In hypoparathyroidism which, biochemically is the exact opposite of hyperparathyroidism, roentgenographic abnormalities might be expected in the form of increased density of bone. Contrary to expectation, skeletal changes are seen uncommonly the reason being that in hyperparathyroidism two opposing influences act upon the skeleton. In this condition the decrease of osteoclastic activity might well cause increased deposition of the bone substance, whereas the impaired intestinal absorption of calcium has an unfavorable influence upon ossification. In most cases of hypoparathyroidism, these two opposing factors are in equilibrium and the skeletal roentgenograms are normal. Occasionally the influence of the poor calcium absorption prevails, resulting in a diminished

density of the skeleton.

This is often specially marked in the spine and extremities (PLATES 14b 15b c) Very rarely the decreased function of the osteoclasts causes a generalized sclerosis of the skeleton, as was present in one of the cases described by Forbes.[8] The latter has drawn attention to an important skeletal anomaly In two of his cases of hypoparathyroidism the width of the lamina dura of the teeth was increased. This is the counterpart of the loss of the lamina dura—a nearly constant sign in advanced hyperparathyroidism.

Albright has recently defended another explanation of the loss of bone substance which from time to time is found in hypoparathyroidism.[1]

Treatment of acute tetany should consist of slow intravenous administration of calcium gluconate until the symptoms are controlled. In digitalized patients, great caution must be exercised in the administration of intravenous calcium, since cardiac standstill has been reported after such combined treatment. Long range therapy can be effectively accomplished by the administration of dihydrotachysterol (A.T 10 or Hytakerol) The main action of A.T 10 consists of increased excretion of phosphate by the kidneys at the same time, the absorption of calcium from the bowel is markedly enhanced. Thus, the effect of parathyroid hormone is mimicked and the increased phosphate excretion results in lowering of serum phosphate levels. Both increased osteoclastic bone resorption and improved absorption of calcium from the intestine lead to elevation of serum calcium. The recommended dosage is 3 cc. (1.25 milligrams per cc.) of A.T 10 daily until the Sulkowitch reaction of the urine become normal. The calcium intake should be increased by the administration of calcium lactate or gluconate, milk as a source of calcium must be avoided because of the high phosphorus-to-calcium ratio An aluminum preparation can be given to diminish phosphate absorption from the bowel. An attempt may be made to produce a mild acidosis, thus increasing the ionization of the serum calcium and thereby diminishing the tendency to tetany

However, since vitamin D is much more active than A.T 10 in increasing absorption of calcium from the bowel, hypoparathyroidism is often treated today with large quantities of vitamin D Usually 8 capsules of 50 000 I U are given until the serum calcium reaches 10 milligrams per cent. Then the quantity is reduced, but the maintenance doses commonly vary between 50 000 and 200 000 I U daily In view of the popularity of the administration of very large doses of vitamin D for the treatment of tetany in every case of hypoparathyroidism with general thinning of the bones the possibility of hypervitaminosis D must always be considered. This iatrogenic hypervitaminosis D however cannot explain all the cases of bone resorption in hypoparathyroidism.

Injections of parathyroid extract also control the manifestations of hypoparathyroidism. Unfortunately this preparation is expensive and the development of antibodies against the extract may in time render such treatment ineffective.

PSEUDOHYPOPARATHYROIDISM

The remarkable condition which Albright designates pseudohypoparathyroidism deserves careful discussion. All the biochemical signs of hypoparathyroidism—hypocalcemia, hyperphosphatemia and decreased urinary excretion of calcium and phosphorus—are found in patients suffering from this disease. The patients have tetany attacks and are often considered to be epileptic, while an x ray of the skull may reveal the presence of calcific deposits in the basal ganglia. In contrast to hypoparathyroidism, peculiar somatic anomalies exist in pseudohypoparathyroidism. The patient usually has a round

moon-face and often carries a perpetual smile. His figure is short and stocky. A remarkable dyschondroplasia of the metacarpals and metatarsals leads to early closure of the epiphyseal disks and thus to shortening of one or more fingers. This anomaly is most frequently encountered in the first, least frequently in the second metacarpal (PLATE 14a). When a normal person makes a fist, the heads of the metacarpals present as knuckles. In a patient with pseudohypoparathyroidism, at the location of the abnormal metacarpals dimples sometimes appear, but never knuckles, when the hands are closed.[8]

Finally, subcutaneous foci of ectopic ossification (PLATE 14a) are much more frequently present in these patients than in patients with genuine hypoparathyroidism. Patients with pseudohypoparathyroidism seem to have a tendency to develop hypertension.

Pseudohypoparathyroidism fundamentally differs from true hypoparathyroidism: in pseudohypoparathyroidism, the structure and *the function of the parathyroid glands* are normal. Allegedly a normal quantity of parathyroid hormone is excreted, but the kidneys fail to respond to this hormone. Both normal persons and patients with hypoparathyroidism react to injections of parathyroid extract by increased urinary excretion of phosphates. No such reaction can be evoked in patients with pseudohypoparathyroidism, not even by intravenous injection of large quantities of the extract.

The resistance to parathyroid hormone may be demonstrated by the Ellsworth-*Howard test.*[7] These authors determined the phosphate content of hourly urine specimens for three hours before and for three to five hours after the intravenous administration in the fasting state of 2 cc. (200 units) of parathyroid extract injection. The normal response is an approximately sixfold increase in urinary phosphate excretion; patients with idiopathic hypoparathyroidism respond with a tenfold increase. Contrariwise, patients with pseudohypoparathyroidism scarcely double their phosphate excretion. Unfortunately present-day authors are rather dissatisfied with the results of this test. The test dose of parathyroid extract has gradually been increased and now varies between 300 to 600 units of parathyroid extract. Even with such large doses the increase of the phosphorus excretion is variable and often cannot be reproduced. Albright nowadays recommends that the serum calcium and phosphorus levels after a series of daily intramuscular injections of parathyroid extract[14] be followed, to demonstrate the difference between hypo- and pseudohypoparathyroidism. All this makes it imperative that resistance to parathyroid hormone should not be diagnosed before the activity of the parathyroid preparation has been demonstrated by eliciting a response in a normal individual.

It is of interest that in pseudohypoparathyroidism, parathyroid extract given either intramuscularly or intravenously causes an increase of serum calcium *and* serum phosphorus. Since in these patients parathyroid extract does not cause hyperphosphaturia, the changes in serum levels of calcium and phosphorus must be due to an effect of the hormone on nonrenal tissue, that is, upon the skeleton.[4]

This result helps to explain why in hyperparathyroidism *hyper*calcemia and *hypo*phosphatemia occur side by side. Parathyroid *extract causes increased osteoclastic bone* resorption. The excess calcium and phosphorus, liberated by the osteoclastic hyperactivity must appear at least temporarily in the blood. Under normal conditions, parathyroid extract also increases the *renal* excretion of phosphorus in normal persons, therefore, the serum phosphorus drops to below *normal levels, while the hypercalcemia* persists (p. 62). In pseudohypoparathyroidism, however the kidney does not respond to the excess of parathyroid extract. Thus, in this condition both serum calcium and phosphorus remain increased after the injection of parathormone.

The recognition of this condition has

ractical importance because the anomalies f calcium and phosphorus in serum and urine of patients with pseudohyperpara hyroidism can be corrected by the administration of vitamin D or A.T 10 (dihydroachysterol) Occasionally, a patient with etany—or "epilepsy"—who does not react avorably to treatment with parathyroid ex ract can be recognized as a case of pseudohypoparathyroidism and can be cured by vitamin D and/or A.T 10

Variations of this syndrome have been described and abortive cases have been reported.[13-14] Albright has observed patients with a round face, dyschondroplasia of the metacarpals and metatarsals, and subcutaneous foci of ectopic ossification, but with normal calcium and phosphorus content of the serum and urine. Since the calcemia and phosphatemia are normal in this syndrome (which Albright has designated pseudo-pseudohypoparathyroidism) no calcification of the basal ganglia takes place.[3]

In all fairness it must be said that such patients do not present any symptoms or signs reminiscent of hypoparathyroidism. It may be of some importance that the pattern of shortening of the metacarpals of these patients appears to correspond to special developmental characteristics. Those meta carpals in which the epiphyses develop latest[4] are most likely to be shortened. The sequence in order of diminishing lateness is I V, IV III, and II The frequency of the changes in the metacarpals of patients with pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism largely adheres to this order, thus suggesting a relationship with other dyschondroplasias. In fact, in the studies of Murk Jansen,[9] published fifty years ago, striking similarities are found between the physical abnormalities (moon-face, brachy dactylism) of his dyschondroplastic dwarfs and of patients with pseudo- and so-called pseudo-pseudohypoparathyroidism. Thus, the somewhat clumsy name pseudo-pseudohypoparathyroidism might in the future perhaps be replaced by the designation dyschondroplasia with soft tissue calcification and ossification," as proposed by McNeely and colleagues.[10a]

Another incomplete form of pseudohypoparathyroidism recently came under our observation [16] The patient was a sixteen year old girl with hypocalcemia, hyperphosphatemia, hypocalciuria and hypophosphaturia. The ensuing attacks of tetany had been masquerading for many months as epilepsy Her stature was short, her face round and broad, her hands, however were normally formed and no roentgenologic abnormalities of the metacarpals were found. No hyperphosphaturia was obtained after the administration of parathyroid extract. An excellent clinical response did follow the administration of A.T 10 A comparable case has been reported by Albright.[3]

References—Chapter 12

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Chapter 13

Paget's Disease of the Bone (Osteitis Deformans)

EIGHT DECADES HAVE PASSED SINCE PAGET described the first cases of osteitis deformans. In that day and age methods of examination were less refined and complicated than in our time. Thus, Paget, investigating the disease which in the future would carry his name had to rely mainly upon inspection and palpation. The adjective "deformans" signifies that Paget could recognize this condition only when characteristic skeletal deformities had developed. He emphasized, for instance, that in his cases of osteitis deformans a grotesque asymmetric deformation of the skull had developed and that the tibias were markedly thickened and bent forward. The gait had become slow and awkward, because the deformity of the femurs obliged the patients to hold their legs wide apart. The spine was shortened, the dorsal and lumbar curves greatly exaggerated.

In contrast to Paget's description, the greater part of the cases of osteitis deformans diagnosed today are completely asymptomatic. Usually the characteristic bone lesions are found incidentally during the galaxy of roentgen examinations employed by modern medicine. And even if the disease causes discomfort, the diagnosis is commonly made by roentgen examination long before the terminal condition described by Paget has developed. Today, the antero-lateral incurvation and shortening of the bones of the lower extremities, the development of a kyphosis with increased dorsal and lumbar curves, the decrease of the body length, the enormous and asymmetric skull are only rarely observed among the large number of cases of osteitis deformans diagnosed by roentgen examination.

The changes in the configuration of the skull should be specially mentioned. In Paget's first case the osteitis deformans was so rapidly progressive that the patient was obliged to buy a larger hat every year. Nowadays it is realized that such a rapid increase of the circumference of the skull is a most unusual finding. All this notwithstanding, even today many physicians upset their patients by repeated inquiries as to a possible increase in the size hat they have been wearing in the course of the last decades. The persistent belief that the diagnosis of Paget's disease can hardly be made without evidence of an increase in the size of the skull, though erroneous, pays homage to the perspicacity of Paget's original clinical observations.

SYMPTOMS AND SIGNS

Aching in the bones is often the first complaint that brings the patient with Paget's disease to his physician. In some cases these pains are very severe indeed, probably due to progressive destruction of bone trabecules. They are only rarely due to compression of nerve roots by fractures of vertebrae. Other signs of Paget's disease are early deafness, pathologic fractures of long bones, pelvis or spine and a sensation of heat caused by the interesting circulatory dynamics of the Paget bone.

Postmortem examination reveals that in contrast to Paget's conclusions, osteitis deformans occurs at least as frequently in the sacrum, pelvis and spine as in the skull and

tibia. *It has also become evident that Paget's disease is at best polyostotic, never generalized. Even in the most extensive cases there are always parts of the skeleton which are free from the disease. As a matter of fact,* involvement of the ribs, the fibulae, the hands or the feet occurs only rarely in Paget's disease. There are exceptions, of course, the calcaneus bone especially (PLATE 19*a*, *b*) and other bones of hands and feet (PLATE 19*c* *d*), less frequently may be affected by osteitis deformans.

Table 3 demonstrates that in Paget's disease certain parts of the skeleton are more frequently involved than others. The similarity of the spread of the disease, both in postmortem and x ray reports, is rather remarkable, because with the latter method earlier stages of the disease are elicited than with autoptic studies. The frequency of localization of Paget's disease in the pelvis, spine, skull and femur, as observed in the two series of Table 3 is also evidenced by other statistics. Involvement of these parts of the skeleton was observed by Collins[4] in 77 per cent and by Dickson et al.[9] in 77 per cent of the bone lesions discovered among patients with osteitis deformans. It must be added that Collins studied the autopsy findings of 46 cases of Paget's disease, while Dixon studied the roentgenograms of 367

TABLE 3

BONE DISTRIBUTION OF OSTEITIS DEFORMANS

A in 138 patients at autopsy[illegible]
B: in 111 patients checked during life with radiography[illegible]

Skeletal Site	*Per Cent of Total* A	B
Femur right	31	37
Cranium	28	33
Sternum	23	?
Sacrum	56	?
Pelvis	22	33
Femur left	15	29
Clavicle	13	3 right 5 left
Tibia	8	6 right 3 left
Ribs	7	4
Humerus	4	8 right 7 left

Localization in spine	*69 patients*	*111 patients*
Spine, lumbar	26	66
Spine, dorsal	17	17
Spine, cervical	7	5

Familial occurrence of Paget's disease *is* not rare[9] Dickson observed the disease in six family members, spread over *four* generations.[4] In Rosencrantz's study seven of 111 patients with *osteitis deformans* had relatives afflicted with the same ailment.[13] In another *series of 32 cases, a familial history* was noted in four instances. Paget's opinion that osteitis deformans occurs almost invariably in individuals over the age of 40 generally still holds true.[4] Exceptions do occur—*occasional* cases of Paget's disease can be diagnosed in pa

tients in their thirties and even younger Such juvenile cases are often but not always, monostotic in nature. It is our impression that in families where Paget's disease is rampant, the disease has a tendency to occur at a younger age. It is of course possible that the members of such families are especially observant as far as changes of the skeleton are concerned.

ETIOLOGY

The etiology of Paget's disease is unknown. Its presence in patients with different endocrine disorders is probably only coincidental. The possibility that an excessive production of growth hormone might be responsible for the etiology of Paget's disease has recently been discussed.[13]

The exceptional finding of a parathyroid adenoma at the autopsy of patients who suffered from Paget's disease must also be ascribed to coincidence. In any case, removal of two normal parathyroids does not result in improvement of the osteitis deformans.[19] The possibility exists that in the future the following facts may help to clarify the etiology of Paget's disease.

1 In horses, a diet of bran, low in calcium, but very rich in phosphorus, causes "big head disease," consisting of swelling of the head, curving of the spine, anorexia, weakness and inability to stand. In this disease microscopic examination reveals skeletal changes which are at least reminiscent of Paget's disease. Low calcium and high phosphorus diet causes in goats the development of osteofibrosis. Later, atrophy and osteoporosis are found.[4]

2. In certain oriental countries where the phosphorus intake is low, Paget's disease is a rarity

3 Parathyroid extract and A.T 10 drugs which increase phosphorus elimination via the kidneys, are known to have a favorable influence upon the pains of patients with Paget's disease.

4 The same holds true for the administration of aluminum acetate, which decreases phosphorus resorption from the intestine.

Thus, the possibility that an excessive intake of phosphorus may contribute to the causation of Paget's disease deserves attention.

BIOCHEMICAL SYNDROME

In Paget's disease serum calcium and phosphorus are nearly always normal, the urinary calcium excretion is usually higher than normal, and the alkaline phosphatase content of the serum is significantly increased. The latter is related to the abundant new formation of bone (p 116) that is present in osteitis deformans. Since rapid reparation of bone also occurs in many other diseases, an increase in the alkaline phosphatase of the serum is not at all pathognomonic of Paget's disease. Nevertheless, the presence of a normal phosphatase content of the serum in a widespread skeletal disease would decidedly militate against the diagnosis of Paget's disease. The more extensive the Paget lesions, the higher the alkaline phosphatase content of the serum. In some cases the serum phosphatase may reach values which are 20 to 30 times higher than normal. In patients with osteitis deformans limited to one or two bones, the serum phosphatase usually remains within normal limits. It has been calculated that in widespread cases of this disease the daily accretion of calcium may be 20 times larger than the normal value of 0 4 gram. The resorption of bone increases accordingly and even exceeds the tremendous accretion.

Acid phosphatase of the serum is not increased in osteitis deformans except in cases with very high alkaline phosphatase. A slight or moderate increase of the acid phosphatase has no diagnostic significance when marked alkaline hyperphosphatasemia exists.

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ROENTGENOLOGIC FEATURES

Roentgenologically Paget's disease is characterized by three features

1 Increase of the total diameter of the affected bones.

2 Thickening and broadening of the cortex.

3 Abnormal architecture of both the cortex and the cancellous bone.

Although the diameter of the bones affected by osteitis deformans is increased, the resistance and elasticity of the involved parts of the skeleton are diminished. The increased tendency to fractures must be closely connected with the abnormal course and orientation of the trabecules of the cancellous bone (p 116) Thus, the so-called "spongy hypertrophy of bone" leads to frequent bowing of *long bones and changes in the contour of affected vertebral bodies.* The remarkable abnormal configuration of the skull, if present, can easily be visualized on the roentgenograms. *Both the external table and the diploë* of the calvarium increase in size and present an abnormal, irregular structure that is often foamy in character Due to these changes of *external table and diploë, the diameter of* the skull cap increases and may measure up to one inch. Calcification of the dura may develop and the paranasal sinuses are often *widely distended. Finally the structure of* the calvarium becomes completely abnormal. Numerous areas of circumscribed sclerosis stand out (Plates 15*a* 17*a*) whereas owing to *widespread resorption of bone the rest of* the skull contains less bone substance. The resulting remarkable coarsely mottled appearance is usually designated a "woolly" or "*cotton-wool*" skull. The sutures are often obliterated. The contours of the foramen magnum are changed and become pear shaped or even heart-shaped. Due to the *softening of the Paget skull,* the cervical spine impinges upon the basis cranii (Plate 15*a*) The posterior part of the cranial base becomes more and more elevated, resulting in "basilar impression" or 'platybasia." Ultimately the base of the cranium is more elevated than the anterior cerebral fossa, causing kyphosis of the base of the skull, or "convexobasia," to develop

In the bones of the rest of the skeleton thickening of the cortex is the outstanding sign, whereas the medullary cavity *often* retains its original width (Plates 16 17*c* 18*c* 19*e*) This leads, just as in the skull cap, to an over all increased diameter of the bone, *an important differential diagnostic point* which distinguishes Paget's disease from many other ailments of the skeleton. Ossifying periostitis occurs very frequently another *factor contributing to the increased diameter* of the Paget bone. The marrow cavity of the long bones, comparable to the diploë of the calvarium, becomes irregular and contains a *new and atypical framework of thick and* course trabecules (Plates 18*c* 19*e*) Ultimately the roentgenologic structure of the Paget bone is completely different from that *of normal bone. Thus emphasizes the astuteness* of the commentary of Butlin, Paget's histologist, that "the structure of the Paget bone appears to have been laid down afresh *on a different plan and in a larger mold.*"[3] Often one long bone in its entirety is affected by the disease (Plate 18*b c*) When, however the lesion is limited to part of a long *bone, the dividing line between the normal* and the Paget bone is usually sharply demarcated in the form of a V Such a V shaped lesion, frequently seen in the tibia, is pathog*nomonic for osteitis deformans.*[1] The joints—and also the symphyses—usually remain uninvolved.

Extensive Paget's disease may exist in the *epiphyseal parts of the bones* adjoining an articulation, while the joint surfaces and the joint fissures remain completely normal. However since the disease occurs mainly in individuals who are over the age of 40 osteitis deformans may complicate a coincident rheumatoid arthritis or osteoarthritis not related to the Paget's disease. When Paget's disease befalls a part of the skeleton which at the same time is affected by osteo-

arthritis, the osteitis deformans frequently develops first in the osteophytes. In Paget's disease of the calcaneus, for example, osteitis deformans of the calcaneus spur is usually prevalent (PLATE 19*b*). Due to the grotesque changes of the osteophytes, the roentgenograms of Paget's disease, complicating arthritis of the spine, may be completely atypical and difficult to interpret, unless osteitis deformans is also present in other parts of the skeleton. In such cases the changes in the configuration of a vertebra affected by Paget's disease may be helpful for the diagnosis. Since Paget bone is less resistant than normal bone, a Paget vertebra is often compressed, leading to a decrease in the vertical dimension. At the same time, the vertebra is extended laterally, both in antero-posterior and lateral views the compressed Paget vertebra overhangs its adjoining neighbors (PLATE 18*a*–*d*).

Paget's disease of the pelvis can usually be recognized by the increased diameter of the pubic and ischial bones (PLATES 16–20). At the same time, the cortex is thickened and the structure of the cancellous portion of these parts of the skeleton is abnormal. Due to the decreased resistance of the Paget bone, the pressure of the femur heads often causes a heart shaped deformity of the inlet of the lesser pelvis (PLATE 21). This is also observed in osteomalacia.

In the later stages of Paget's disease, sclerosis of the affected bones often develops, (PLATE 17*c*)—especially the pelvis (PLATE 21), vertebrae (PLATES 17*b*, 18*d*) and femurs. This may lead to new difficulties in interpretation. Osteoblastic metastases to the pelvis due to a carcinoma of the prostate (PLATE 47) may at first view closely resemble osteosclerotic Paget's disease. In contrast to the findings in osteitis deformans (PLATES 16–20), sclerosis of the pubic or ischial bones by osteoblastic metastases usually does not lead to an increased diameter of the affected bones, except in the terminal stages. Furthermore, in the initial stages of Paget's disease an increase in the diameter of the *cortex* of the bones is found. In contrast, the initial stages of osteoblastic carcinoma metastases, especially of carcinoma of the prostate, present as small, ill-defined areas of sclerosed bone. These sclerotic patches gradually increase in size and coalesce until at last a uniform density of the whole affected bone results. The increased acid phosphatase of the serum and the presence of tumor cells in the bone marrow obtained by puncture of the iliac crest are final proof in the differentiation of pelvic metastases of prostate carcinoma from Paget's disease.

Pseudocystic cavities may be found within the parts of the skeleton affected by Paget's disease (PLATE 19*e*). These cavities, usually filled by fat, have sometimes led to speculations about similarities between Paget's and Recklinghausen's bone disease. Needless to say, these two diseases can be differentiated without any difficulty, both roentgenologically and biochemically.

When bowing of the long bones occurs in Paget's disease, the cortex of the convex side of the bone is commonly thickened. Occasionally on the roentgenograms of the curved bones one or more short, fissure like transverse lines of rarefaction, 1–2 centimeters long and 1–2 millimeters thick, may be seen in the cortex, always situated on the convex side of the bone. Dickson et al. found such fissures four times in the femur and three times in the tibia in 367 cases of Paget's disease.[6] The fissures must be distinguished from the fine cracks due to incomplete fractures as described by Milkman in osteomalacia. In the latter condition, the fissures are symmetric and occur in roentgenologically *normal* bone. In Paget's disease the fissures are not symmetric and the cortex around the fissures is altered by the osteitis deformans. The cortex is never completely interrupted by these fissures because the subperiosteal layer of the cortex remains intact. These incomplete fissures, which usually are lined by a thin layer of dense bone, may well represent areas of proliferation of osteoid tissue surrounding incomplete fractures.

Cementosis—proliferation of dental cement around the roots—can sometimes be visualized on the dental roentgenograms of patients with osteitis deformans.[3,10] Since cementosis is rare in other bone diseases, hyperplastic deposition of cement on the dental roots (PLATE 17*d*) justifies a presumptive diagnosis of Paget's disease.

As a rule, the roentgenologic diagnosis of Paget's disease is simple, but difficulties may arise when only one or two sclerotic vertebrae are found (PLATE 17*b*). In such cases the differential diagnosis between Paget's disease, osteoblastic metastatic tumor, Hodgkin's disease, aleukemic megakaryocytic myelosis and Albers-Schönberg's disease may be impossible.[21] However, when a broadening of the cortex, i.e., of the terminal plates, and an abnormal architecture of the sclerotic vertebra are found (PLATE 18*a*) the presence of Paget's disease is highly probable. The same holds true when a compressed vertebral body is enlarged in both lateral and antero-posterior directions (PLATE 18*d*).

HISTOLOGY AND VASCULARITY OF PAGET BONE

In the normal skeleton the osteons are surrounded by concentrically arranged bone lamellae which are separated by plates of osteoid (see p. 2). On histologic sections stained with Ehrlich's acid hematoxylin, these osteoid plates appear as dark blue lines, so-called cement lines. The normal daily wear and tear of the skeleton takes place along these cement lines. In Paget's disease, osteoclastic bone destruction is immediately followed by deposition of abnormal coarse trabecules. As a result, the regular "lamellar circumhaversian" arrangement is changed into a mosaic consisting of numerous irregular patches of newly constructed bone, glued together by heavily staining cement lines. These mosaics of degenerated abnormal bone structures, first described by Schmorl,[24] are found nearly exclusively in the lamellar bone of Paget's disease; they rarely occur in Recklinghausen's bone disease. Between the irregularly oriented coarse fibered trabecules, hyperemic fibrous tissue proliferates which replaces the normal cellular bone marrow.

In his original reports Paget emphasized that the bone in osteitis deformans is hyperemic. This early observation has been confirmed repeatedly by clinical observation. When Paget's disease is localized in bones which are covered by skin and fat alone, both abnormal heat and edema can often be elicited. The tibia and the skull are the skeletal parts which can best be used to demonstrate these phenomena. On the other hand, this phenomenon cannot be studied in the parts of the skeleton that are surrounded by large muscular masses. The increased temperature of a tibia with osteitis deformans becomes very evident when both limbs of the Paget patient are exposed to room temperature for one hour. The temperature of the skin of the healthy tibia then goes down considerably, whereas the skin over the tibia of the Paget extremity remains hot. This can easily be checked with the aid of a thermocouple.[16]

The increased vascularity of the Paget skeleton leads to abnormal circulatory dynamics. Edholm, Howarth and McMichael[7] found in one patient with Paget's disease a remarkably high cardiac output of 13.3 liters per minute (normal, 4 to 6 liters), together with cardiac failure, high pulse pressure, diminished vascular resistance and venous congestion. The elevation of the cardiac output depended mainly upon a decreased peripheral vascular resistance.

Insufflation of cuffs placed around the extremities affected by osteitis deformans to a pressure above the systolic caused slowing of the pulse, decrease of the cardiac output and slight rise of the diastolic pressure. The same signs are observed after partial occlusion of the afferent vessels of an arteriovenous aneurysm. McMichael and associates suggested that since a large arteriovenous aneurysm was not present, multiple small arteriovenous shunts in the Paget bone might be responsible

for the observed findings. The authors then demonstrated that the "hyperemia" of the affected bones is due to an abnormally rapid blood flow, which may be twenty times greater in the affected bone than in its normal counterpart. No wonder that the oxygen content of the venous blood which returns from a Paget's bone is abnormally high. Later they emphasized that these circulatory signs develop only when more than one third of the skeleton is affected and when the disease is actively progressing as evidenced by an alkaline phosphatase content of the serum exceeding 33 Bodansky units per hundred centimeters.[8] Lequime and Denolin came to comparable conclusions.[13] They pointed out that in most cases of Paget's disease the cardiac output was normal during rest. Only during exercise did the output rise to abnormally high levels. Apparently in osteitis deformans, just as in the presence of an arteriovenous aneurysm, during effort an excessive volume of blood returns suddenly to the right ventricle. The French investigators also stipulate that an increase of the cardiac output at rest can only be expected in particularly active and extensive cases of osteitis deformans. The abnormal local circulation in the diseased bones is an important factor in the causation of the cardiac dilatation and the vascular failure frequently found in patients with Paget's disease.

The work of McMichael et al was so interesting and it was presented so convincingly that many clinicians accepted the existence of arteriovenous communications in Paget bones. However, it has been impossible to actually demonstrate such shunts in histologic preparations. Rütishhauser et al. found a tremendous increase in the number and diameter of arterioles and arteriolar capillaries in Paget bone.[14] When intramedullary phlebography is performed, larger and more numerous blood vessels appear to be present in Paget bone than in normal bone. Also in the diploë of the Paget skull large blood lakes could be visualized.

Thus, it is generally agreed that the abnormalities of the circulatory dynamics in extensive Paget's disease reported by McMichael and his group actually exist. Even if the presence of multiple arteriovenous communications has not been demonstrated histologically, the decrease of the arteriolar resistance caused by arteriolar dilation has the same physiologic effect as if such shunts were actually present.

COMPLICATIONS

Severe headaches are commonly observed in patients with Paget's disease. Usually in such cases widespread changes are found in the roentgenograms of the calvarium, while the remarkable hot temperature of the skin overlying the skull cap can distinctly be felt by palpation.

Paget stressed that the mental faculties of his patients remained unaffected. This was true even in cases where thickening of the skull had developed. However neurologic syndromes in Paget's disease have often been reported.

In platybasia or convexobasia the encroachment of the upper cervical vertebrae upon the posterior cerebral fossa, together with the changes of the contour of the foramen magnum, may cause compression of the medulla and adjoining parts of the brain. In such cases, paralysis of cranial and cervical nerves or degeneration of columns and tracts of the cord may ensue. Sudden death occasionally occurs due to compression of the medulla. The changes in the shape and histologic structure of the petrous bone may result in narrowing of the semicircular canals, the saccule and the utricle. The cochlear nerve is often thinned and the aqueduct of the vestibule closed. Thus, deafness and vertigo are frequent signs.

Fractures after an insignificant trauma are a common complication of Paget's disease and occur especially in the upper third of the femur and the pelvis. The fractures are

often transverse in character and heal well. If nonunion occurs in a pathologic fracture of a Paget patient, the possibility of secondary sarcoma development must be seriously considered.

Dickson et al. mention that 22 of their 367 cases of Paget's disease suffered from nephrolithiasis. We have found comparable figures among our patients. The resorption of bone that always accompanies Paget's disease causes hypercalciuria and may lead to nephrolithiasis. On the other hand, it must be realized that an intravenous pyelography visualizes not only the kidney, pelvis and ureters, but also the sacrum, pelvis and lumbar spine. These parts of the skeleton are very frequently affected by Paget's disease. In other words, roentgenologic examination of patients with nephrolithiasis reveals not only the presence of renal stones, but also a possible involvement of the skeleton by Paget's disease. It follows that the simultaneous occurrence of renal stones and osteitis deformans may be purely coincidental.

DEVELOPMENT OF SARCOMA IN PAGET BONE

Paget's disease by itself rarely endangers life, unless sarcoma develops in one of the diseased bones. Paget found a tumor in 5 of his 8 patients at autopsy in 2 of them a sarcomatous degeneration of osteitis deformans was present. Brailsford[1] found malignant changes in 6 of 154 Rosenkrantz in 8 of 111 patients with Paget's disease. Lower figures, that is, an incidence of about 2 per cent, are also quoted, and only 3 of Dickson's 367 cases developed sarcoma. Finally, two series of 138 and 116 cases respectively have been published without one instance of sarcoma.[14,15] Recently we have seen more and more cases of sarcoma in bones affected by Paget's disease. Sarcomatous bone degeneration occurs most frequently in the femur (PLATE 20) humerus,[16] skull, tibia, scapula, spine and pelvis (PLATE 21) Roentgenologically the initial phase of the sarcomatous degeneration often presents as a subcortical medullary destructive lesion, which later develops into an osteolytic area in the cortical part of the bones. Sclerotic tumors have occasionally been observed. The tumor has indistinct borders (PLATE 21) without periosteal reaction (PLATES 20 21) or joint involvement. Sometimes a soft tissue mass can be made out which is only rarely pulsating in character. Every pathologic fracture in a Paget patient requires a careful roentgenologic study to exclude the presence of a sarcoma.

Sarcoma developing in Paget's disease is commonly osteogenic. Rarely does a fibrosarcoma or a chondrosarcoma[18] develop under these conditions. Sixteen of the 19 cases described by Sherman and Soong[17] were osteogenic sarcomas, one was a fibrosarcoma. One of these osteogenic sarcomas was sclerotic in nature. Sarcoma development in Paget's disease is not a purely coincidental finding, because osteogenic sarcoma is an uncommon disease in patients over the age of 50. Not only is osteitis deformans present in about one fourth of the patients with osteogenic sarcoma who are older than 50 years, but in these patients the sarcoma develops only in bones affected by osteitis deformans. Osteogenic sarcoma does occur in patients with osteitis deformans below the age of 50 but only rarely. Sarcoma of the calvarium in older patients is nearly always a complication of Paget's disease. This localization was found 3 times in a series of 19 cases of Paget sarcoma.[17] Intracranial invasion by osteogenic sarcoma in Paget's disease has been observed. Cerebral extension is still rarer and has been reported only twice.[8] It is remarkable how often in Paget's disease sarcomatous growth develops almost simultaneously in more than one of the bones affected by osteitis deformans. Sherman and Soong, however commented on the possibility that metastases of Paget sarcoma to the skeleton may be more common than is usually thought.[17] The lungs, too are frequently the site of metastases.

The prognosis of all types of sarcoma in Paget's disease is very poor, the average survival period being no more than one year.

The diagnostic difficulties which may develop are well illustrated by the following observation. In a 45 year old man who was admitted with complaints of pains in the right femur, roentgen examination revealed sclerotic Paget's disease of the left pelvic bones. The pain at the right side was due to an osteolytic lesion in the right femur, which at one place had eroded through the cortex (Plate 20). The bone in and around the femur lesion did not appear to be affected by Paget's disease. Biopsy showed the presence of an osteogenic sarcoma. Microscopically, mosaic structures were found in some of the bone trabecules. Therefore, although no osteitis deformans of the right femur could be demonstrated roentgenologically, this patient nevertheless suffered from a Paget sarcoma.

TREATMENT

No effective treatment of Paget's disease has yet been found. Many authors have reported transient alleviation of the bone pains after roentgen-ray irradiation of the diseased parts of the skeleton. Vitamin D and ultraviolet ray therapy have led to some improvement in a few cases, although this fortunate outcome may not be accepted as proof of a direct influence of vitamin D upon Paget's disease. It seems at least possible that these patients could have suffered from a moderate degree of osteomalacia, superimposed upon the original Paget's disease, as a result of long-standing lack of exposure to sun and diminished appetite (see p. 67). The signs of osteomalacia in these patients would naturally disappear with adequate vitamin D treatment, although the underlying osteitis deformans remained unchanged.

The beneficial effect of parathyroid extract on the pains from which Paget patients occasionally suffer has been mentioned. Davis[4] has had an unfavorable result in one patient, but several of our patients have been relieved of pain by daily injections of 1 cc. of parathyroid extract. The calcium content of the serum must be regularly ascertained during this treatment, although on the whole Paget patients show little or no tendency to hypercalcemia during treatment with parathyroid extract.[18] Parathyroid hormone has been standardized by determination of the degree of hypercalcemia it produces. There is reason to believe that the modern preparations cause less phosphaturia than the extracts which were available 25 years ago. Since parathyroid extract probably influences Paget's disease by increasing phosphaturia, more than 1 cc. of the drug may well be necessary. The same favorable results have been obtained with dihydrotachysterol.[18]

Helfet[11] has given aluminum acetate to patients with various bone diseases in order to precipitate the phosphate in the intestine as aluminum phosphate, thereby reducing the phosphorus absorption. In view of a possible influence of excessive phosphorus intake upon Paget's disease (p. 113) we follow Helfet's line of thinking and usually prescribe a diet low in phosphorus: no milk, cream, cheese, whole grain cereals, sweetbreads, or liver; small amounts of meat, fish, chicken. In addition, one tablespoon of Basal-jel is given four times daily together with small doses of Hytakerol. If necessary, injections of parathyroid extract are administered.

Recently the treatment with adrenocortical extract, which at one time was a popular method for the therapy of osteitis deformans, has been revived in the form of cortisone administration. In the hands of some observers this preparation has an almost magic effect upon the pains of these patients. It seems that with corticosteroid treatment not only clinical improvement, but also disappearance of the mosaic patterns in the diseased parts of the skeleton can be obtained.

As far as surgical procedures are concern

ed, in the initial stages of compression of the cord by Paget's disease of the spine, laminectomy must certainly be considered. Between 1923 when Wyllie reported the first case of this syndrome, and 1951 39 such cases have been reported.[21] In 20 of these cases laminectomy was performed, and 14 of the patients improved.

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Chapter 14

Osteoporosis Circumscripta Cranii

Moore,[4] in 1923 and Schüller,[6] in 1926, drew attention to a disease of the skull that is characterized by the presence of one or more translucent areas in the calvarium. It has been recognized that this disease, nowadays designated osteoporosis circumscripta cranii, is not a rarity at all. On the contrary, osteoporosis cranii is rather frequently observed among patients with Paget's disease, probably also in polyostotic fibrous dysplasia of the skull and occasionally in other bone diseases.

ROENTGENOLOGIC FEATURES

At roentgenologic examination the affected and decalcified areas are clearly defined by serrated and undulating borderlines. The lesion is commonly localized in the frontal and parietal areas, less frequently in the occipital parts of the skull. The disease appears to spread fan-wise, starting either from the anterior or the posterior pole of the skull. Within the involved parts of the skull the remnants of trabecular structure, islands of sclerotic bone, vascular markings and suture lines are nearly always visible (Plates 17*a* 28*a*)

In the earlier phases of the disease roentgen examination shows that the external table and the diploë are more deeply involved than the internal table. The lesion is not halted by cranial suture lines. Usually, large areas of the calvarium, sometimes even practically all the bones of the skull, are affected (Plate 28*a*)

In the later phases of the disease the differentiation of osteoporosis cranii from other diseases of the skull does not offer any difficulties. When, however the osteoporosis circumscripta is limited to a small area, confusion with other bone diseases — e.g lipoidgranulomatosis of the skull—would seem possible.[4] Whereas in osteoporosis circumscripta no complete resorption of the tables is found all the other diseases of the skull which have a somewhat similar appearance actually destroy the tables.

In cases where the patches of sclerotic bone within the osteoporosis circumscripta lead to a cottonwool appearance of the skull (Plate 28*a*) the condition is usually ascribed to Paget's disease. This rule, however, also has exceptions (Plate 28*b*)

In rare cases, no trace of bone can be discerned on frontal or lateral views of the lesion, and the impression may be obtained that in the affected area a complete resorption of bone has taken place. Even in such cases, tangential radiographs always reveal that paper thin inner and outer tables are still present. Rossi and Pisani[5] are of the opinion that when such large areas of pure osteoporosis are present in the skull, signs of Paget's disease never develop either in the osteoporotic area of the calvarium or in the rest of the skeleton. They feel that this purely porotic lesion is not a *manifestation* of osteitis deformans.

PATHOGENESIS

Moore, and especially Sosman,[7] emphasized that connections must exist between osteoporosis circumscripta and Paget's disease. As a matter of fact, in many patients whose skulls exhibit clear-cut areas of osteoporosis circumscripta, roentgenologic examination of

the rest of the skeleton reveals widespread Paget's disease. Nevertheless, the osteoporosis circumscripta rather frequently is the only manifestation of osteitis deformans.[1]

Osteoporotic circumscripta of the skull has often been found in patients with leontiasis ossea—a disease which may be caused either by Paget's disease or by polyostotic fibrous dysplasia (see p. 140). It follows that osteoporosis circumscripta may also be encountered in the latter disease. Finally a few cases of *osteoporosis circumscripta cranii* have apparently occurred in patients with typical Recklinghausen's bone disease,[8] in whom removal of the parathyroid tumor led to considerable improvement of the skull lesion. Therefore, although osteoporosis circumscripta cranii occurs frequently in osteitis deformans, it is not necessarily identified with this disease.

PATHOLOGY

Until recently, only few pathologic studies of circumscribed osteoporosis of the skull had been reported. The scanty communications all agreed that this lesion presented an early stage of Paget's disease. Nevertheless, several clinicians felt that other possibilities had to be considered.

For some time it was believed that the lesions found in osteoporosis circumscripta could be caused by a hemorrhagic infarction of the skull.[3] The large arteriolar lakes which are characteristically present in the Paget bone could well predispose to the development of such an infarction.

The gross features of the classical cases of infarction of the skull described by Schmorl are somewhat similar to the findings in circumscribed osteoporosis. In both cases, the sharp edges of the purplish reddish diseased part clearly separate the lesion from the surrounding ivory-colored normal bone. At histologic examination Schmorl found masses of dead bone, evidently the result of avascular necrosis.

It seems highly improbable that in the areas of circumscribed osteoporosis necrotic bone could be present, since the latter would present at roentgen examination as dense sclerotic masses (p. 188). Collin and Winn,[1] who carefully examined five skulls with osteoporosis circumscripta cranii, found, in agreement with the older reports, only areas of patchy or focal osteitis deformans. The lesion is different from the common manifestation of Paget's disease, because the bone resorption far exceeds the hasty regeneration characteristic of osteitis deformans. Inasmuch as no dead bone was found in any of these five cases, the presence of an infarction seems to be excluded. On the other hand, Collins and Winn found lesions of Paget's disease in other parts of the skeleton in only one of their five cases of osteoporosis circumscripta of the skull. In the other four cases, no Paget changes could be discovered in the rest of the skeleton.

These results confirm the conclusion of Sosman, who suggested that in many cases osteoporosis circumscripta cranii might well be "the absorptive or destructive phase of Paget's disease at work with the productive phase held in abeyance."[7] As mentioned above, Rossi and Pisani[8] do not agree with this statement. In their opinion, large purely osteoporotic areas in the calvarium not containing any sclerotic bone patches represent a special skeletal lesion that is not connected with Paget's disease.

Until now there is no pathologic proof that osteoporosis circumscripta can be caused by polyostotic fibrous dysplasia, even if radiographic evidence seems to point to this possibility (PLATE 28*b*)

CLINICAL FEATURES

The clinical manifestations of *osteoporosis circumscripta cranii* are usually minimal, although occasionally such patients complain about severe headaches. This is in sharp con-

trast to the widespread and seemingly serious anomalies which can be visualized by roentgenologic examination.

In one of our patients with leontiasis ossea we followed the uninterrupted progress of circumscribed osteoporosis for 20 years (Plate 28). Here, Paget's disease was undoubtedly the underlying condition. Ultimately, multiple osteosarcomas developed in the maxillary bone and in the calvarium (p. 140).

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Chapter 15

Hand-Schüller-Christian's Disease, Letterer-Siwe's Disease, Eosinophilic Granuloma

In the course of the first forty years of this century three seemingly different clinical entities were described Hand Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma. These three syndromes, it seems, are not only closely related, but may well represent three different stages of the same disease. Nevertheless, certain differences exist, so much so that the clinicians and pathologists who first described the three "diseases" had no inkling that they could have a common etiology

HAND-SCHÜLLER CHRISTIAN'S DISEASE

In 1893 Hand described a syndrome consisting of (1) multiple round bone defects in the skull (2) exophthalmus—often bilateral and (3) diabetes insipidus. Although this disease is prevalent among children and young adults, older adults may also be affected, though less frequently

Schüller in 1915 attributed this syndrome to pituitary dysfunction, because one of his patients also suffered from dystrophia adiposogenitalis. Christian, in 1919, observed the gradual disappearance of the disease in a 5 year old child. In this patient, eleven years after the original diagnosis had been made, abnormal signs could no longer be elicited. Rowland, in 1928 made an important contribution by demonstrating that the lesions of Hand-Schüller-Christian's disease consist mainly of nests of foam or xanthoma cells. These foam cells are studded with birefringent esters of cholesterol. A few years later Chester[2] pointed out that the large sheets of proliferating histiocytic xanthoma cells are surrounded by granulomatous tissue. In view of these histologic findings, Chester called the disease a "lipoidgranuloma of the bones." In the older lesions, the foam cells and the granulating tissue disappear to be replaced by hard fibrous tissue. Even then, polarization microscopy of the frozen sections still reveals the presence of cholesterol esters.

Lipoidgranulomatosis of the bones is not caused by a primary disturbance of the cholesterol metabolism. As a matter of fact, tuberous skin xanthomas, the characteristic lesions in typical xanthomatosis, have hardly ever been observed in Hand-Schüller-Christian's disease. The reverse is also true, in typical xanthomatosis of the skin with marked hypercholesterolemia, lipoidgranuloma of the bones does not occur Moreover the bone lesions in Hand-Schüller-Christian's disease are granulomatous in nature and cannot be identified with a true xanthoma. Finally hypercholesterolemia is usually absent, and the extensive study of Layani, Ducroquet, and Laudat[8] did not reveal any clear-cut disturbance of the cholesterol metabolism in this disease.

CLINICAL PICTURE

The first signs of Hand-Schüller-Christian's disease often consist of pains in the back, thorax, hip or thigh, and may sometimes even consist of a pathologic fracture. In other

cases, a localized swelling of the skull develops first. Headaches occur frequently. In about half of the cases, diabetes insipidus leading to excessive thirst and polyuria is present. Exophthalmus, either unilateral or bilateral, and infantilism are somewhat less frequently observed. All the symptoms and signs of the disease result from the proliferation of the lipoidgranulomas. This process causes the round areas of bone resorption in the calvarium and invades the retro-orbital space, giving rise to exophthalmus. The development of such lesions in the body and the stalk of the pituitary or in the neighboring diencephalic centers (tuber cinereum) is followed by diabetes insipidus or by infantilism, and sometimes also by excessive obesity and adiposogenital dystrophy. Apart from the calvarium, other parts of the skull may be involved. In the mandible the lipoid granulomas cause progressive loosening and loss of teeth, in the petrous part of the temporal bone, deafness and otitis media. Even meningitis may ensue, though this is rare.

Whereas in the original publications the cranio-hypophyseal localization of the lipoid granulomas was stressed, it has gradually been recognized that the same pathologic lesion may involve other parts of the skeleton, the skin and the internal organs. Cases of Hand-Schüller-Christian's disease with additional osteolytic lesions in the spine, pelvis, ribs, mandible, clavicles, femora and other bones of upper and lower extremities have been frequently described.[1] Skin eruptions may occur. The cutaneous lesions are often papular and hemorrhagic in character and consist, at microscopic examination, of a proliferation of foam cells.

Extraskeletal localizations of lipoidgranuloma have also been observed in the liver, renal pelvis, brain, spleen, lungs, mesentery, brain, and external genital organs.[1,11,14] Localization of the lipoidgranuloma in the wall of the aorta and the large vessels explains the extensive and premature arteriosclerosis which has often been mentioned in the autopsy reports of such patients.

In about fifteen per cent of the cases of Hand-Schüller-Christian's disease the granuloma affects the interlobular septa of the lungs. Since the resulting interstitial fibrosis starts simultaneously in the adventitia of the pulmonary capillaries and in the interlobular connective tissue of the lungs, an "alveolo-capillary block" with dyspnea and cyanosis often ensues. Obstructive emphysema may also be present, which frequently leads to "spontaneous" pneumothorax. Thus, due to the diffusional and ventilatory disturbances of the respiration, lipoidgranulomatosis of the lungs has a serious prognosis.

In later years more and more cases of lipoidgranulomatosis occurring in older persons have been reported.[14] The disease starts more slowly in adults than in children. In the older age groups diabetes insipidus, an osteolytic bone lesion or dyspnea due to pulmonary fibrosis frequently are the initial signs. Serum calcium, phosphorus, alkaline phosphatase and blood lipids are normal.

In one 55 year old patient who was admitted for exophthalmus and diabetes insipidus, we found at autopsy extensive lipoidgranulomatous areas in the eyebrows, adipose tissue of the orbits, in the fatty tissue between the right auricle and the right ventricle, in the wall of the superior vena cava near its entry into the right auricle, mesentery, peripelvic tissue of kidney, left ethmoid, in several vertebrae and in the left half of the pituitary.[14] A bilateral hydronephrosis was present due to dilatation of the renal pelvis as a result of the scarring of the peripelvic lipoidgranulomas. Although a lipoidgranuloma in the adipose tissue of the hilum of the kidney is not uncommon, hydronephrosis due to scarring of a peripelvic lipoidgranuloma must be very rare. In this case a lipoid granuloma in the mesentery presented as a large tumor in the left upper part of the abdomen which, at palpation, gave the impression of an enlarged kidney.

ROENTGENOLOGIC FEATURES

The osteolytic lesions in the skull in Hand-Schüller-Christian's disease are round or oval

in shape. The disease starts in the diploë but usually erodes either the internal or the external tables. The borders of the lesions are well defined. Rarely a faint osteosclerotic rim is present. The size of the lesions varies between 1 and 10 centimeters. In some cases only one or two lesions are seen in other cases they are numerous (PLATE 22*a*) Erosion of the floor of the sella turcica and of the orbital structures is often present, with or without osteolytic lesions in the upper and lower jaw It may be difficult to decide whether osteolytic lesions of the skull are due to lipoid granulomatosis or to other diseases, such as metastatic malignancies, lymphomas and especially epidermoid cysts. The latter lesions, however, are surrounded by a marked sclerotic and scalloped rim (PLATE 22*b*)

Roentgenologic lesions may also be found in other flat bones, e.g., pelvis, scapulae, ribs and vertebrae. The granulomatous areas in the long bones present as cystlike lesions, localized most frequently in the femur, but also in the humerus, radius, ulna and other parts.

Lipoidgranulomatosis of the lungs can be visualized as a submiliary spread or a diffuse reticular fibrosis. Such a micronodular pulmonary dissemination in patients who obviously are not suffering from miliary tuberculosis can easily be confused with a pulmonary spread of Boeck's sarcoids.

It should be specially mentioned that at autopsy lipoid granulomas may be found in the skeleton in cases where roentgenologic examination had failed to demonstrate any skeletal lesion during life. This existed in the patient mentioned on page 125 where microscopic examination revealed lipoidgranulomas in the ethmoid bone and in several vertebrae, although the roentgenograms of the skeleton had appeared to be completely normal.

Diagnostic difficulties arise when lipoid granulomatosis of the bones does not appear in the typical cranio-hypophyseal localizations but *only* in other parts of the skeleton. Without careful biochemical study these cases may be confused with Recklinghausen's disease. As a matter of fact, the roentgenograms of the lipoidgranulomatous skeletal areas, other than in the skull, resemble the x ray picture of the cysts, sometimes even of the giant cell tumors, found in Recklinghausen's bone disease. For the correct diagnosis a biopsy is usually necessary In such cases the tentative diagnosis of multiple areas of osteitis fibrosa may well be entertained until the histologic diagnosis is available.

These differential diagnostic problems have been recently discussed again by Weissman et al.,[10] in whose patient only two areas of lipoid granulomatosis were found in the tibiae. Nevertheless, the lipoidgranuloma must also have invaded the sella turcica and the surrounding brain tissue, because this patient had discrete signs of dystrophia adiposogenitalis.

PROGNOSIS AND TREATMENT

Until now many hundreds of cases of Hand-Schüller-Christian's disease have been reported. Dangerous complications result from damage to the hypothalamus, the pituitary or the diencephalic centers. In addition, due to cicatrization of the lesions in the interlobular septa, a cor pulmonale and a "capillary-alveolar block" often develop. These different complications are responsible for the frequent fatal termination of the disease, especially when it occurs in children. In 1951 Froehlich reported that 20 per cent of 330 patients collected from the literature had died.[8] Fortunately, in many cases, just as in Christian's original patient, the bone lesions, the diabetes insipidus and the exophthalmus may vanish spontaneously

Roentgen-ray therapy often has a favorable influence upon the lesions. Unfortunately the effect of such treatment is purely local, only too often new lipoid granulomas develop in different parts of the body shortly after termination of the radiation therapy There are also cases which are refractory to x ray treatment. Then, a trial with corticosteroid treatment is justified.

LETTERER SIWE'S DISEASE

In Letterer-Siwe's disease, multiple areas of a proliferating histiocytic granuloma are disseminated throughout the skeleton, the skin and the visceral organs. In contrast to the findings in Hand-Schüller Christian's disease, no secondary lipidization of the histiocytic granuloma takes place in Letterer-Siwe's syndrome. Microscopically, the lesions consist *solely of proliferating reticulum cells.* Furthermore, whereas Hand-Schüller-Christian's disease mainly befalls children and young adults, the greater part of the patients with Letterer-Siwe's disease are young infants below the age of two or three years.[18] Finally the clinical course and also the prognosis of both diseases are different. Letterer-Siwe's syndrome presents in most cases as a severe constitutional disease. One of the first manifestations is frequently a purpuric or ecchymotic cutaneous eruption, often combined with superficial ulcerations of the mucous membranes of the mouth and adjacent areas. The little patients are very sick, with marked loss of weight, persistent spiking or low grade fever, occasionally associated with a tendency to secondary infections. The spleen and lymph nodes are enlarged. Common signs are progressive anemia and normoblastosis of the peripheral blood, both due to displacement to the bone marrow by proliferating histiocytes and possibly by hypersplenism.

In such cases a sternal puncture may reveal diffuse infiltration of the bone marrow with histiocytes. Involvement of the wall of the smaller bronchi may give rise to obstructive emphysema, as was found in the child described by van Creveld and van der Poorten in 1936.[18]

In most cases of Letterer-Siwe's disease, multiple destructive lesions in the skeleton *with a predilection for the* calvarium are present. The roentgenograms of the skull closely resemble those obtained in Hand Schüller-Christian's disease. Other bones, especially the metaphyses of the long bones, are also often involved. In 9 of 46 patients Kennedy[8] has followed for nearly 3 decades, *the osteolytic lesions were limited to the skull.* In 32 patients the skull and other bones were the sites of histiocytic granulomas. Only in 5 patients were cranial lesions absent.

In Letterer-Siwe's disease the babies may be so desperately ill that the bone lesions remain completely in the background. The prognosis of this disease is very unfavorable, the mortality rate is extremely high. Only in exceptional cases, after x-ray treatment, has the condition gradually changed into typical *Hand-Schüller-Christian's disease.*

Fisher has presented evidence that possibly in some cases of Letterer-Siwe's disease a complicating inflammatory process may be an all important indication for determining the prognosis.[3] In one case of an apparently fatal form in a two year old Negro boy, blood cultures proved the existence of a blood stream infection by a paracolon bacillus. Adequate antibiotic treatment led to a cure of the paracolon sepsis and to a remarkable improvement, possibly even to healing of the disease.

Thus, in all cases of this syndrome, even if no positive evidence of an infection can be obtained, a trial with roentgen treatment and antibiotics should not be foregone. Cortisone treatment has also been recommended. Unfortunately, favorable results are rare.

EOSINOPHILIC GRANULOMA

Closely related to Hand-Schüller-Christian's disease and Letterer-Siwe's disease is the so-called *solitary or eosinophilic granuloma of bone.* In 1940 Otani and Ehrlich[13] reported a group of patients suffering from an osteolytic skeletal lesion which they labeled "solitary granuloma of the bone." Histologically Otani and Ehrlich found that

this lesion consisted of a granuloma formed by proliferating histiocytes mixed with leukocytes, eosinophils and osteoclasts. Necrotic areas, hemorrhages and bone reparation were present.

In the same year Jaffe and Lichtenstein[14] also studied this lesion. They stressed the prevalence of the accumulation of eosinophilic cells among the sheathlike collections of histiocytes for this reason they designated the lesion an "eosinophilic granuloma of the bone." The same bone disease had been described in 1929 by Finzi as an "eosinophilic myeloma," in 1930 by Mignon as a "granulation tumor" and in 1938 by Schairer as an "osteomyelitis with eosinophilic reaction."

Eosinophilic granuloma occurs mainly in young individuals, more often in males than in females. This lesion has also been observed, though less frequently in older individuals, even in patients in the near sixties. By 1955 more than 190 of such eosinophilic granulomas had been described. The lesion is not necessarily solitary multiple localizations have been found in about one fourth of the cases reported. In one patient, 25 different eosinophilic granulomas were counted.

In eosinophilic granuloma, either solitary or multiple, the presenting signs are pain and swelling of the affected bone or bones, and, occasionally malaise, fever, loss of weight and leukocytosis. Headache may be present when the skull is affected. Rarely a pathologic fracture is the first manifestation of the disease, but often the lesion does not cause any clinical symptoms or signs. Occasionally especially in the skull and ribs, the granulomas may break through the cortex, perforate the skin and cause a fistula. Eosinophilia of the peripheral blood varying between 4 and 10 per cent is not rare. Serum calcium and phosphorus are normal, and an increase of the alkaline phosphatase of the serum is uncommon. Pain in the back, muscle spasm and rigidity tenderness on percussion and kyphosis may result when an eosinophilic granuloma causes collapse of a vertebra. Neurologic signs caused by an eosinophilic granuloma have been observed.

ROENTGENOLOGIC FEATURES

The roentgenologic picture of a solitary eosinophilic granuloma may suggest a bone cyst, giant cell tumor myeloma, metastatic or primary bone tumor or even a Ewing's tumor The lesion starts in the medullary part of the bone, progressing towards the cortex from the inside, so that the cortex is gradually thinned, ultimately even eroded and perforated. Often there is clear-cut expansion of the diaphysis. When the continuity of the cortex is compromised, pathologic fractures may occur The granuloma may perforate the cortex so precipitously that the suspicion of a malignancy is entertained, until biopsy reveals the presence of an eosinophilic granuloma. After a pathologic fracture, the granuloma usually invades the surrounding soft tissue. Two cases of a bone sequestrum present within the eosinophilic granuloma have been described.[17] The lesion is especially frequent in the skull, ribs, pelvis (PLATE 22c) vertebrae (PLATE 23a b c) humerus and femur It occurs both in the diaphyses and epiphyses of the extremities, but it is decidedly much more frequent in the diaphysis than in the distal parts of the bones. Carpal, metacarpal, tarsal and metatarsal bones are hardly ever affected. Compression of the vertebra results when these histiocytic granulomas are localized in a vertebral body whereas the adjacent intervertebral disks remain intact.

In this connection, an interesting point has been brought up by Compere and associates.[4] They observed four cases of so-called vertebrae planae as described by Calvé which at biopsy were proven to have been caused by the presence of an eosinophilic granuloma. Compere et al. therefore are of the opinion that vertebrae planae of Calvé are the result of localization of an eosinophilic granuloma in a vertebral body

Freely translated, Calvé's description of the roentgenologic characteristics of vertebrae planae runs as follows "Only the vertebral body is involved. The adjacent disks both below and above the involved vertebra are intact and may even be wider than the next

disk spaces. The vertebra is evenly flattened and has the dense appearance on the roentgenogram of a silver dollar."

This description clearly fits the roentgenologic picture caused by an eosinophilic granuloma of a vertebral body (PLATE 23a b c). Until now, the etiology of vertebrae planae has always been mysterious. Vertebrae planae cause a syndrome reminiscent of the initial phases of a tuberculous spondylitis with restriction of the mobility of the spine, pain on pressure of the diseased area, indirect pains after sudden movements, and gibbus formation. Calvé himself did not believe that this disease was tuberculous in origin. Since the intact intervertebral disks exclude this possibility, Calvé was of the opinion that such vertebrae planae were due to a vascular necrosis. Other authors considered an epiphysitis or a trauma as a possible cause of this vertebral disease. In the light of the available data it seems highly probable that, as suggested by Compere et al., vertebrae planae are due to the localization of an eosinophilic granuloma in a vertebral body

TREATMENT

The outlook in eosinophilic granuloma, without signs of Letterer-Siwe's or Hand Schüller-Christian's disease, is in general favorable. Recurrence after currettage, surgical removal or roentgen therapy is unusual. However new lesions may well develop. In children and young adults, the danger exists that the localized form of the eosinophilic granuloma may change into the acute form of the disease, i.e., Letterer-Siwe's disease. The potential dangers of an eosinophilic granuloma are demonstrated by the experience of Kennedy who had the opportunity to follow 45 cases of reticuloendotheliosis since 1927.[8] The outcome was favorable in 29 cases. Four patients were still under treatment and ten died. Of the latter, one patient had lipoidgranulomatosis and six, Letterer-Siwe's disease, but three had suffered from an eosinophilic granuloma.

DISCUSSION

In all three ailments discussed above, histologically a low grade inflammatory process—a granuloma—exists. The characteristic feature of this granuloma consists of a widespread proliferation of histiocytes—reticuloendothelial cells which have acquired phagocytic activity These histiocytes are mainly derived from the adventitia of the smaller blood vessels. In Hand-Schüller-Christian's disease the proliferating histiocytes have phagocytized lipids from the surrounding tissues in eosinophilic granuloma, phagocytic manifestations remain in the background, but there is a striking increase of eosinophilic leukocytes. In Letterer-Siwe's disease there exists purely a histiocytic proliferation.

Until now none of the collective names proposed to cover all three syndromes has satisfied the semantics of every clinician or pathologist. Both obvious terms, "histiocytic granuloma" and reticuloendotheliosis," lack the necessary specificity, since these names would also be a fitting description of the histologic characteristics of tuberculosis, typhoid, histoplasmosis, sarcoidosis, and even Hodgkin's disease. The difficulties in terminology are clearly illustrated by the experience of Lichtenstein.[14] After an exhausting and soulsearching discussion of this problem, he had to resign himself to naming these three pathologic entities 'histiocytosis X."

The boundaries between the three diseases are not as sharply drawn as was originally thought. Close connections evidently exist, since patients with typical lipoidgranuloma of the skull may suffer from a nonlipid histiocytic infiltration of the lung parenchyma. The histiocytic proliferation is the primary progress, the lipidization of the histiocytic granuloma by cholesterol infiltration being only a secondary phenomenon. In the second stage the proliferating histiocytes phagocytize the lipoids, which are liberated in the course of the breakdown of the surrounding normal tissue. Thus, lipoidgranulomas can only develop in areas where fat is abundant, as for

instance, in the bone marrow In the lungs, where fat tissue is only scarce, the granulomas are remarkably poor in lipoid. Even the usually fatal Letterer-Siwe disease may change its character The anemia and the normoblastosis due to displacement of the bone marrow by histiocytes may gradually disappear Several instances are known where an acute form of Letterer-Siwe's disease gradually changed into a chronic Hand-Schüller-Christian disease.

Patients with a typical eosinophilic granuloma have been observed to suddenly develop a papular, erythematous skin rash which, at biopsy, proved to consist of numerous genuine histiocytic granulomas. Such patients usually died shortly afterward from a full-blown Letterer-Siwe syndrome. In other patients with eosinophilic granuloma, diabetes insipidus and a fine nodular type of pulmonary infiltration[3] were found. In other words, a transition of an eosinophilic granuloma to a Hand-Schüller-Christian disease had occurred. Histologically lipidization of the histiocytes had taken place and the eosinophiles had vanished—a process which seems to be accelerated by roentgen treatment. On the other hand, patients with Hand-Schüller-Christian's disease have been recorded who suffered from a skin rash which at biopsy proved to consist of a histiocytic granuloma without any cholesterol infiltration. This combination clearly points to the close connections existing between Hand-Schüller-Christian's disease and the Letterer-Siwe syndrome.

Keizer and Rochat[7] described a patient in whom a destructive bone lesion in the scapula together with a submiliary spread in the lungs were present. Autopsy revealed the presence of all three histiocytic syndromes simultaneously Histologically not only malignant reticuloendothelioses but also lipoid-granulomatosis and eosinophilic granulomatosis were found.

Nowadays, eosinophilic granuloma is defined as the localized, rapidly developing early phase of the histiocytic disease. The chronic disseminated form of this special histiocytosis presents as Hand-Schüller-Christian's disease. The acute or subacute disseminated form of the disease is represented by Letterer-Siwe's syndrome.

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Chapter 16

Osteitis Fibrosa Disseminata (Albright) or Polyostotic Fibrous Dysplasia

THE REMARKABLE CLINICAL CURE WHICH Mandl, in 1926 had obtained in a patient with Recklinghausen's bone disease initiated an *avalanche of* parathyroid explorations in patients with multiple or generalized bone lesions. Around 1930 it became evident that true Recklinghausen's bone disease with generalized absorption of bone, multiple cysts and giant cell tumors due to hyperparathyroidism was often confused with another bone disease in which cystlike areas in the skeleton were also found. Thanks to the efforts of different groups of clinicians, a new syndrome was recognized which is characterized by the following findings

1. At x ray examination one or more cystlike lesions are found. At the site of these osteolytic areas pathologic fractures are apt to occur
2. Except in the areas where such pseudocysts are localized the cortex of the bones is completely normal there is no *generalized* affection of the skeleton.
3. Deformations of the bones are frequent, usually as the result of pathologic *fractures.*
4. The calcium and phosporus content of the serum is normal. As a rule, the alkaline phosphatase content of the serum is also normal occasionally it is moderately increased.
5. Biopsy reveals that the cystlike lesions consist *of masses of firm fibrous tissue.* At histologic examination these lesions can *usually* be distinguished from the osteitis fibrosa present in Recklinghausen's bone disease, Paget's disease, and other skeletal affections.
6. Cutaneous pigmentation in the form of saw toothed, brown, nonelevated patches is often present.
7. In females, premature sexual development frequently occurs. In males, precocious puberty is a great rarity

This syndrome can easily be differentiated from Recklinghausen's bone disease because both the *generalized* osteitis fibrosa and the characteristic biochemical syndrome of hyperparathyroidism are absent. We reported the first case in 1932—a ten year old girl whose menarche had started when she was *only seven.*[80] *This girl had multiple,* small, brown naevi spread over her face and chest. Our second report, published in 1934 concerned a male, thirty five years old. He had such extensive areas of pigmentation on the mucous membranes of lips and mouth that we went to great pains to exclude the presence of Addison's disease.[81] In both these patients multiple cystlike areas were found *in the bones, and both* had suffered multiple pathologic fractures. Biopsies of the osteolytic lesions revealed the presence of osteitis fibrosa.

Until 1925 osteitis fibrosa had always been considered a specific disease this was the reason that prior to that year Recklinghausen's *disease* and Paget's disease were believed to be closely allied—if not identical—ailments. The new discovery—that Recklinghausen's bone disease was a manifestation of hyperparathyroidism—completely changed this state of affairs. Now osteitis fibrosa was

understood to represent a secondary reaction of bone—a mere sign—and just as little a disease entity as fever, anemia, or gastric achlorhydria.

Thus, when in 1932 biopsy of the lesions of the newly described syndrome revealed the presence of osteitis fibrosa, it seemed necessary to delve further into this problem in order to find the latter's etiology. We were greatly interested, therefore, to discover after prolonged examination, that islands of xanthoma cells full of double refractile cholesterol esters were present amid the fibrous tissue of these osteolytic areas. Needless to say that only by examination of frozen unstained sections with the polarization microscope could the presence of cholesterol esters be proved. Neither of our two patients showed signs of Hand-Schüller-Christian's disease, that is, of the craniohypophyseal localization of lipoid granulomatosis. Nevertheless, we ventured to classify the syndrome described as a form of "lipoidgranulomatosis of the bones without signs of Hand-Schüller-Christian's disease."[11,1]

It is noteworthy that three biopsies had to be performed in the second patient before the diagnosis could be established. The older lesions all showed osteitis fibrosa; only when a fresh lesion in the femur was examined microscopically could the accumulation of xanthoma cells, surrounded by hard fibrous tissue, be discovered. We thus gained the impression that the purely fibrous lesions represented the end stage of the disease.

In 1937 Albright[3] also reported this syndrome and emphasized that in this disease both premature sexual development and extensive cutaneous pigmentations with jagged contours frequently occur. He named the syndrome "disseminated osteitis fibrosa with pigmentation and precocious puberty," in contrast to the generalized osteitis fibrosa found in Recklinghausen's bone disease. In later years the designation Albright's disease has been commonly used.

Albright observed that in addition to bone destruction, the presence of marked overgrowth of bone is characteristic for the disease.[1] This overgrowth can often be seen in the skull, especially at the base of the occipital bone (PLATE 28b).

Lichtenstein,[18] in 1938, and Lichtenstein and Jaffe,[19] in 1942, pointed out that pigmentation and sexual precocity were not constant findings in Albright's disease, whereas all such patients did show changes of the bones. In order to do justice to the prevalence of the skeletal manifestations, Lichtenstein then coined the designation "polyostotic fibrous dysplasia," which was meant to indicate that the main characteristic of this disease consists of typical changes of bone structure. At the same time, this name was intended to define the nature of the gross and microscopic changes found in the skeletal system in this disease. The name polyostotic fibrous dysplasia has been generally accepted, although the disease is not necessarily polyostotic, but may remain limited to only one bone.[16] In this monostotic form of the disease, endocrine disturbances have never been found. Abnormal cutaneous pigmentation, however, has been reported in four such cases.[18]

CLINICAL SYNDROME

In female patients with this disease, precocious puberty is much more frequently the presenting feature than skin pigmentation (PLATE 27b). The areas of pigmentation are not elevated, have irregular contours and never itch. These pigmented patches are found mainly on the back, shoulders, arms, buttocks, thighs and scalp. The remarkable early initiation of sexual maturation—the precocious puberty mentioned above—is often the first sign of the disease. In one infant menstruation started at the age of two months, hypertrophy of clitoris and labia was observed in a child of nine months, while formation of typical mammae appeared in a child four years old. One female patient was

thirty four years old when the first pathologic fracture drew attention to the skeletal disease. Pigmentation had been present at birth and menstruation had begun at the age of seven. Other endocrinologic signs, though rare, have been observed—for instance acromegalic features and gynecomastia. Skeletal precocity is present in most patients.[8] These patients are tall during childhood, but since the epiphyseal disks close prematurely, the adults with this disease are often short in stature.

In some of Albright's patients all the bone lesions were localized unilaterally, but such localization is relatively rare. A few observations, previously published as "unilateral osteodystrophia fibrosa" and as "unilateral Recklinghausen's disease," evidently belong to this Albright" syndrome. Gradually, it has become evident that this disease occurs more frequently than Recklinghausen's bone disease.[19]

Because the condition has occasionally developed in patients who had been severely jaundiced soon after birth, it has been speculated that failure of the liver function plays a role in the etiology Severe gastrointestinal disturbance in the neonatal period and hyperthyroidism have been observed in such patients.[23]

ROENTGENOLOGIC FEATURES

In agreement with our original statement, the cystlike areas in the skeleton (Plate 26*a* *b*) are still considered the outstanding feature of the disease. These areas are mainly localized in the diaphysis and metaphysis and usually do not affect the epiphyses.[18] However one or more long bones occasionally are involved in their entirety Often, irregular calcification or ossification can be visualized within the cystlike areas. In none of the patients with this disease has involvement of all the different components of the skeleton been elicited there are always extensive parts of the skeleton where the bone is completely normal. In nearly all instances involvement of the femur is present (Plates 25*a* *b* 26*a*) Manifestations in the skull are common. Asymmetry of the face, caused by swelling of the zygoma is a frequent occurrence. Other common sites of these areas of osteitis fibrosa[19] are ribs (Plate 23*d*) pelvis (Plates 25*a* 26*a*) tibia, humerus (Plate 26*b*), fibula, radius (Plate 24) ulna, metacarpals (Plate 24) metatarsals, and phalanges (Plate 24) The involvement of metacarpals or metatarsals is hardly without exception multiple (Plate 24) The frequency of the latter localization is diagnostically important because in Paget's disease, metacarpals and metatarsals are usually but not always, free of disease (Plate 19*c* *d*) The cortex of the cystlike areas of osteitis fibrosa is markedly thinned due to endosteal erosion from within (Plates 24, 25*a* *b*) At the same time, owing to the marked proliferation of abnormal fibrous tissue the contour of the bone is broadened and expanded. Sometimes the cystlike areas have a trabeculated structure and resemble giant cell tumors[16] (Plate 23*d*)

The skeletal structure is weakened bowing of bones is frequently observed (Plate 25*b*) Deformation of the pelvis (Plate 25*a*), sometimes leading to a heart-shaped configuration of the innominate line (Plate 26*a*) may result. Apposition of the major trochanters against the iliac bones (Plate 26*a*) is often present. Pathologic fractures readily occur These fractures heal easily but often leave considerable deformities. Although most authors stress the rarity of subperiosteal and cortical pseudocysts in this disease, such lesions decidedly occur (Plate 27*a*) Periosteal reaction is relatively rare, but older lesions may show osteosclerosis. The overgrowth of bone at the occipital squama is typical for the disease (Plate 28*b*) Sometimes the metaphyseal part of the epiphyseal cartilage is irregular suggesting that islands of cartilage have been incorporated into the diaphysis. Premature closure of epiphyseal disks with cessation of growth is commonly observed. The lamina dura of the teeth remains intact.

HISTOLOGY

Lichtenstein and Jaffe[13] describe how the gritty, firm connective tissue present in the cystlike lesions is arranged in interlacing bundles and whorls. Minute spicules of immature fiber bone, irregular in size, form and distribution, abound. Sporadic islands of *hyaline cartilaginous* tissue are commonly found. Osteoclasts are only rarely seen and osteoclastomas and true cysts are absent. *Lichtenstein suggests that in this disease the* bone forming mesenchyma produces a proliferating fibrous tissue instead of normal cancellous bone. Thus, the particles of fiber bone and cartilage present in the lesions are formed by direct osseous and cartilaginous metaplasia of the proliferating connective tissue. Using special histologic technics, Valls[22] and associates later confirmed that the bone trabeculae of the lesions consist of matted fibers, which are formed by the reticuloendothelial cells present in the osteitis fibrosa. In the opinion of these authors, only the presence of cartilaginous masses distinguishes polyostotic fibrous dysplasia from other bone anomalies in which osteitis fibrosa occurs. It seems doubtful, however that this statement is completely correct.

COMPLICATIONS

The outlook in far the greater part of the cases of polyostotic dysplasia is favorable. Usually there is no further progress of the disease after adult life has been reached. Roentgenograms made of our second patient in 1946, thirteen years after his disease had been discovered, showed that the disease process had become stabilized. As a matter of fact, this patient felt completely well in 1947[18] and had not suffered a pathologic fracture since 1934 Exceptions, however occur and progressive bowing of an affected bone has been reported In older lesions sclerosis of the bone is not uncommon.

Rapid and exuberant growth of one of the bones affected by polyostotic fibrous dysplasia has occasionally been observed (Plate 23*d*) In one of Jaffe's patients, the right eighth rib ultimately attained the size of a football. Neither grossly nor microscopically could evidence of malignancy be found in the resected specimen. Nevertheless, sarcomatous degeneration of fibrous dysplasia does occur The first case of this syndrome, which we reported in 1932 as lipoid granulomatosis,[20] developed a sarcoma of the femur in 1936.[17] Since then, five other cases of sarcomatous degeneration of fibrous polyostotic dysplasia have been reported. We recently saw a new case of sarcoma development in fibrous dysplasia of the upper part of the femur in a 60 year old woman. In this patient the pseudocyst had been unroofed more than 30 years previously, and the cavity had been filled with bone chips.

A certain number of cases of leontiasis ossea, a disease which previously was considered to be a special form of Paget's disease, are actually due to polyostotic fibrous dysplasia.[24]

ETIOLOGY

Everyone agrees that the patients we reported in 1932 and 1934 are examples of a well defined syndrome, later described by Albright. However opinions have differed as to the etiology Our initial contention that these two cases (which nowadays would be termed "Albright" disease or polyostotic fibrous dysplasia) presented a form of lipoid granulomatosis without craniohypophyseal localization has encountered considerable criticism.

In the opinion of Jaffe and Lichtenstein, polyostotic fibrous dysplasia should be considered to represent a congenital anomaly of bone formation due to a *disturbance of* the function of the bone forming mesenchyma.

In view of the lesions widespread nature, Albright speculated that this disease might be caused by a congenital anomaly—e.g., disseminated embryonic defects—of the central nervous system. In one of his cases the abdominal and cremasteric reflexes were abolished at the side on which the bone lesions and pigmentation were present. Occasionally a positive Babinski reflex and other neurologic signs have been observed. In one autopsy performed on a patient with this disease, one mammillary body was abnormally small. In the adjacent tissue one accessory nucleus was found. In another autopsy hyperplasia of the basophilic cells of the pituitary was present. At the autopsy of the first patient we described, Dustin and Ley[8] found marked astrocytic ghosts in the molecular layer The underlying cortex was intact, except for a moderate increase of macro nuclei in the glia of layers V and VI. In the white substance, too a moderate proliferation of the macroglia seemed to be present. In other autopsies no lesions of the central nervous system could be elicited.

Albright, and also Lichtenstein and Jaffe, strongly disagree with our view that cases of Albright's disease or polyostotic fibrous dysplasia could be burnt-out cases of lipoid granulomatosis of the bones. They emphasize that in a granuloma, inflammatory cells must be present which are not found in the lesions of polyostotic fibrous dysplasia. On the other hand, they do not deny that xanthoma cells may occur in the fibrous bone marrow of patients with this syndrome. However they agree with Willis,[14] who states that the presence of xanthoma cells in fibrous osteitis is not significant and may occur as a result of degeneration after trauma. In their opinion, these accumulations of xanthoma cells are the result of fatty degeneration and should not be considered pathognomonic of lipoidgranulomatosis.

We have always defended our initial contention that Albright's disease was closely related to xanthomatosis because at the time, we had been informed of the results of the autopsy of our first patient. Even the most critical authors have accepted this girl with numerous pseudocystic lesions, multiple brown nevi and an early menarche, as a classical case of polyostotic fibrous dysplasia.[30] She died of a sarcoma in 1937 and Dustin Sr, in studying this tumor and its metastases, found it to be a true xanthosarcoma, full of sudanophilic substance and double refractile cholesterol esters. Because of the war publication of the detailed report of the autopsy results was delayed. In the meantime, Dustin Sr passed away, and it was not until 1951 that the details of the autoptic findings were published by Dustin Jr and Ley[8] The colored photos of their excellent article leave not the slightest doubt that this patient, who had presented all the signs of polyostotic dysplasia, including pigmentation, early menarche and osteosclerosis, died of a xanthofibrosarcoma. As mentioned above, the sarcoma cells were full of a sudanophilic substance which was double refractile if examined with the polarization microscope. The larger and more abnormal the nucleus of the sarcoma cells, the more cholesterol esters were found in the cytoplasm. This tumor also contained immature and cartilagenous osseous tissue. After the autopsy Dustin Sr had confirmed the diagnosis of lipoidgranuloma. The younger authors were so impressed by the absence of any histologic signs of inflammation in the nonmalignant, hard and fibrous osteolytic lesions that they were unwilling to consider the lesion as a granulomatous process. They did not believe that old lipoid granulomas can be completely transformed to fibrous masses, and they concluded that in this, our first case, the possibility of a granuloma—and also therefore, of a lipoidgranuloma—must be rejected. At the same time, however, they state that in view of the xanthomatous character of the terminal sarcoma, the significance of the islands of foam cells within the osteitis fibrosa of patients with Albright's disease can no longer be disregarded. They agree that these

xanthoma cells full of cholesterol esters cannot be the end result of fatty degeneration of the osteitis fibrosa alone.

Dustin Jr and Ley also emphasize that it is impossible to find sudanophilic and double refractile substance in bone after decalcification. They graciously remark that at the autopsy of this patient, too, the examination of non-decalcified bone would have been foregone were it not for the fact that since 1932, we had been emphasizing the significance of the islands of foam cells present in the areas of osteitis fibrosa. In the future, frozen sections of non-decalcified material of biopsies of fibrous dysplasia lesions should be regularly examined with the polarization microscope for the presence of double refractile substance. Then the importance of the xanthomatous character of this disease would certainly be better appreciated.

Prior to a discussion of the observations accumulated in the literature that seem to confirm the latter statement, a few remarks are in order concerning the alleged differential diagnostic importance of the osteosclerosis that may develop in Albright's disease.

Albright,[1] and also Froehlich [7] have insisted that osteosclerosis does not occur in lipoidgranulomatosis. Contrary to this opinion, Cavanagh and Russell[4] recently reported two cases of lipoidgranulomatosis in two older individuals in one of whom marked osteosclerosis was present. In addition, these authors brought out that osteosclerosis was a feature in the three original cases where, for the first time, the designation lipoid granuloma was used! In 1949 we had already reported a patient with marked and extensive osteosclerosis of a large part of the skeleton in whom biopsy of a fresh lesion demonstrated the presence of a lipoidgranuloma.[18] The old osteosclerotic lesions of this patient with proven lipoidgranulomatosis of the skeleton had been diagnosed by very competent radiologists as polyostotic fibrous dysplasia. Thus observation confirmed our original contention that the older lesions of this disease show osteitis fibrosa, and t lipoidgranuloma can be discovered on fresh lesions are examined microsc This statement was confirmed by Ducroquet, and Laudat.[11] They foc osteitis fibrosa at the biopsy of the n tensive, older cystlike lesions in their with Albright's disease. A year and later a new cystlike decalcification de in the trochanter A biopsy of this fres performed at our insistence, revea presence of large areas of foam c of double refractile material, surrou fibrous scar tissue.

Mondor and associates[14] who, n described a typical case of Albrigh drome, performed two biopsies at quest, one of which was done on lesion. They did not find any xantho tissue. But six years later they found i sary to perform a bone transplanta one of the lesions, and this time they lipoidgranuloma amid the fibrous ti

Cases of burnt-out lipoidgranulo have been reported which are com to our observations. In one patie Albright's disease and typical bone several soft, ill-defined, avascular granulomas, 1 to 2 centimeters in were found in the perirenal fat ne hilum of the enlarged left kidney In holz's article[19] on polyostotic fibrous dy clear-cut islands of xanthoma cells are edly mentioned. In another case of Al disease, the tissue removed from a "l cyst" of the tibia contained numero of foam cells which stood out clearly sections stained with scarlet red.

During the last two years, the r of observations emphasizing the impo of lipoidgranulomatosis in the etiol polyostotic fibrous dysplasia has m rapidly In a recent case of this disease of xanthomatosis were found at biops in the humerus and tibia.[3]

Harriman and Millar[8] describe a v of fifty years who presented the roen logic signs of polyostotic fibrous dy

The right frontal bone, the base and vault of the skull, right femur, right tibia, and right fifth metacarpal bone were involved. In addition, there were discrete areas of brown pigmentation. Histologically, all the characteristics of polyostotic fibrous dysplasia were present. In addition, however, the areas of osteitis fibrosa contained large sheaths of typical foam cells, full of birefringent cholesterol esters. Cholesterol was also found in the interstices of the mature, old fibrous tissue, as in the case of old lipoidgranulomas.

Finally, the observations of Landoff,[10] who followed a patient with lipoidgranulomatosis of the skeleton over the course of nineteen years, deserve attention. His patient presented all the typical signs of polyostotic fibrous dysplasia with characteristic roentgenologic lesions, hyperostosis of the skull, patchy pigmentations and slight hyperthyroidism. The histology of the old lesions in this patient seemed to indicate the presence of polyostotic fibrous dysplasia. However here again biopsy of the younger lesions revealed large accumulations of foam cells which actually dominated the histologic picture.

Landoff also emphasized that in polyostotic fibrous dysplasia, careful examination of decalcified, fixed and stained histologic sections is not sufficient. He agrees that it is necessary to stain frozen sections of the biopsies for the presence of fat and to search these sections with the polarization microscope for birefringent cholesterol esters. This may perhaps explain why at the autopsy of several patients with polyostotic fibrous dysplasia no trace of lipoidgranuloma has been found.

In summary, then, there exists a well defined clinical syndrome wtih cystlike lesions of the skeleton, without signs of generalized resorption of bone, without the biochemical syndrome of hyperparathyroidism, and frequently with brown pigmentation of the skin which, in females, is often associated with premature puberty Both Albright and Jaffe and Lichtenstein have stressed the possibility that this disease, designated Albright's syndrome or polyostotic fibrous dysplasia, could be congenital in nature. However, the close relationship between this polyostotic fibrous dysplasia and lipoidgranulomatosis of the bones cannot be negated. There is at least one group of patients with all the clinical and roentgenologic signs of polyostotic fibrous dysplasia in whom xanthomatosis of the bone is an outstanding finding The presence of osteosclerosis or of pigmentation is not sufficient reason to exclude a lipoidgranuloma. In this connection, it should be kept in mind that the presence of xanthomatosis of the bone can be correctly diagnosed only if frozen sections of cancellous bone are stained with Sudan and examined with the polarization microscope.

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Chapter 17

Leontiasis Ossea

CLINICAL AND ROENTGENOLOGIC FEATURES

In leontiasis ossea a marked increase in the size and thickness of one or more bones of the face and calvarium exists. Occasionally, the skin overlying the diseased bone may be swollen. The name leontiasis ossea, coined by Virchow, indicates that the facial deformity may ultimately lead to a leonine appearance.

The disease often starts in the maxillary bone. Inspection of the oral cavity reveals a smooth, hard bluish and painless swelling of the alveolar process of the upper jaw At the same time, bulging of the infraorbital part of the maxillary bone frequently exists. Sometimes the bone changes in leontiasis ossea remain confined to the maxilla, but usually the mandible, zygoma, the base of the skull, nasal, ethmoid and especially the wings of the sphenoid bone (Plate 27*c*) are also involved. Leontiasis ossea of the jaws, occurring in infants and children, has been distinguished as cherubism.

In the calvarium, the frontal and parietal bones are more frequently affected than the temporal and occipital bones. In the later stages of the disease, the skull and face may be transformed into a shapeless mask. Compression of the nasal cavity by the proliferating bone causes respiratory difficulties the lacrimal ducts may become occluded, leading to a tenacious, purulent lacrimation. The maxillary sphenoidal and frontal sinuses are often filled by soft spongy bone, which reduces the sinuses to narrow fissures. Difficulties of mastication appear secondary to involvement of the temporomandibular joints. Anomalies of speech have been reported. The swelling of the orbital bone leads in many cases to unilateral or bilateral exophthalmus and to displacement of one or both eyes. Narrowing of the optic foramen, compression of the optic nerve and blindness also occur (Plate 27*c*) Headache, convulsions and mental aberrations, in our experience, occur only rarely

On roentgen examination the bone lesion (osteitis fibrosa) can often be visualized in the form of an irregular network of swollen, calcium-poor bone trabecules which has replaced the normal bone structure (Plate 28*a* *b*) In other cases the diseased bone exhibits marked mottled sclerosis. Osteosclerosis is especially seen in the bones of the middle cranial fossa. The coexistence of leontiasis ossea with osteoporosis circumscripta cranii has frequently been reported (Plate 28*a*)

In doubtful cases it is of importance to study the wings of the sphenoid, which form part of the posterior wall of the orbit. Very often, swelling or sclerosis of one of the sphenoid bones is the first sign of the disease (Plate 27*c*) In one third of the cases there is only unilateral involvement of the skull, a condition designated as hemicraniosis. Marked asymmetry of the face is present in the latter condition.

Serum calcium and phosphorus are normal, but when the disease has spread over a major part of the skull the alkaline phosphatase may be increased.

ETIOLOGY

The term leontiasis ossea is purely descriptive, *the malformation may well be caused* by different diseases In many cases of leontiasis ossea histologic examination of the diseased bone reveals osteitis fibrosa and mosaic structures with irregular and excessive new bone formation. In such cases, leontiasis ossea must be a manifestation of Paget's disease. In other patients, however evidence can be presented which seems to militate against this assumption.

The outstanding localizations of leontiasis ossea are present in the facial part of the skull.[14] Contrariwise, in Paget's disease of the skull the calvarium is mainly affected. The bones of the face commonly remain normal, although involvement of the mandibles occurs more frequently than is generally believed.[1] Whereas Paget's disease usually occurs in or after the fourth decade of life, leontiasis ossea nearly always develops in younger persons, often shortly after puberty Both these points are well taken. Nevertheless, we have frequently seen that typical leontiasis ossea which had started during puberty was caused by typical Paget's disease. In some such patients, osteoporosis circumscripta cranii with characteristic cottonwool structure later develops (PLATE 28*a*) In others, typical Paget lesions are found in other parts of the skeleton. In cases of leontiasis due to Paget's disease, the localization of the disease in the facial bones must be the reason that patients seek medical help much earlier than when the osteitis deformans develops in the calvarium This is comparable to the common observation that a pathologic fracture often leads to the discovery of Paget's disease in a young individual. Without the pathologic fracture, the disease might have persisted for many years before the complaints would have been sufficiently serious to justify radiologic examination.

In one of our patients with leontiasis ossea, we were able to follow the progress of the circumscribed osteoporosis of the calvarium over the course of twenty years (PLATE 28*a*) The ultimate cottonwool appearance of the calvarium of this patient leaves no doubt that Paget's disease was the cause of the skull changes, although in this case, too, the first changes of the face had been observed during puberty In addition, large numbers of mosaic structures were present in all biopsies of this patient. The only other skeletal manifestations were localized in the calcaneus and in the third metacarpal bone of the right hand. The serum calcium and phosphorus were normal, the alkaline phosphatase of the serum very high. Ultimately multiple osteosarcomas developed in the right maxillary bone and the calvarium. Metastatic lesions appeared in the lungs, and the patient died 14 months after the first signs of the malignant degeneration had become manifest.

Sarcomatous degeneration in leontiasis ossea must be rare. Only two observations of the development of a fibrosarcoma in this disease can be quoted.[3,4]

It is our impression that most cases of leontiasis ossea are manifestations of Paget's disease. Occasionally, however, leontiasis may develop in full-blown polyostotic dysplasia. In such cases, sclerosis and malformations of the different bones of the skull occur which may ultimately lead to the clinical picture of leontiasis ossea. Sclerosis of the base of the skull, bone proliferation in the sphenoid wings (PLATE 27*c*), narrowing of the optic foramen, and exophthalmus may all be present. But in such cases other signs of polyostotic fibrous dysplasia can usually be elicited, e.g., serrated skin pigmentations, early menarche, hyperostosis of the occipital bone (PLATE 28*b*) and cystlike lesions in the skeleton of the extremities. In addition, roentgenologic signs of Paget's disease, such as cottonwool changes in the calvarium and typical lesions in the peripheral skeleton, are always absent.

Certain incomplete cases of leontiasis ossea in young persons—e.g., thickening and sclerosis of the alveolar process of the mandibula—may well be due to monostotic forms of polyostotic dysplasia. But before this diagnosis is considered, the presence of Paget's disease must be excluded. Occasionally, it cannot be decided whether or not an incomplete form of fibrous dysplasia is the cause of a malformation of maxilla or zygomatous process.

Many decades ago Virchow voiced the opinion that leontiasis could be caused by an inflammation of the bones of the skull that ultimately results in sclerosis. Although this observation was subsequently challenged, the old master's findings have been reaffirmed by a recent report of cases of leontiasis ossea due to a true sclerosing osteitis.[4]

A special form of leontiasis-like deformation of the skull may be seen due to the development of multiple osteomas. This osteomatosis of the skull seems to be fundamentally different from true leontiasis ossea due to osteitis fibrosa. Special mention must be made of the observation of three generations of one family, where both osteomatosis of the skull and congenital polyposis with secondary carcinomatosis of the colon occurred simultaneously.[5]

In genuine Recklinghausen's bone disease due to hyperparathyroidism, the development of cysts and osteoclastomas in the facial bones will only rarely result in the formation of a leontiasis-like face. In these exceptional cases, the diagnosis can be made by the biochemical syndrome that characterizes hyperparathyroidism.

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Chapter 18

Bone Changes in Hemolytic Anemias

THE ERYTHROID HYPERPLASIA OF THE bone marrow, a characteristic feature of all hemolytic anemias, often leads to changes of the bone. The three hereditary hemolytic conditions in which bone changes have been extensively studied are (1) Cooley's anemia, also known as erythroblastic anemia, target cell anemia, thalassemia, or Mediterranean anemia (2) sickle cell anemia, or drepanocytic anemia and (3) chronic hemolytic jaundice, familial acholuric jaundice, or spherocytic anemia.

Important discoveries recently have shed light on the specific and abnormal hemoglobins which are present in the different hemolytic anemias.[7-9] With the use of electrophoretic methods normal hemoglobin-A can be distinguished from many different varieties of abnormal human hemoglobin.

Hemoglobin F fetal hemoglobin, is present in several hereditary hemolytic anemias, especially in thalassemia.

Hemoglobin-S is found in sickle cell anemia and in the sickle cell trait.

Hemoglobin-C differs electrophoretically both from normal hemoglobin-A and from hemoglobin-S and does not cause sickling. When hemoglobin-C is present in the red blood cells, target cell formation is prominent.

Hemoglobin D can be distinguished normal hemoglobin-A only by its el phoretic pattern. Hemoglobin-D is el phoretically identical with hemoglo but does not cause sickling When l globin-S and D are present in the patient, both sickling and a hemolytic a result. Many more abnormal hemog have been described, e.g E to J Ofte abnormal hemoglobins are present taneously in one patient.

In most cases of hemolytic anem which proliferation of erythroblastic is prevalent, an abnormal hemoglo found. The proliferating bone marrow change the architecture of the skeleton, marked in Cooley's anemia and least m in spherocytic jaundice. Sickle cell a has an intermediate position. In adc patients with these hemolytic anemias present developmental anomalies o skeleton. The latter congenital chang most marked in spherocytic anemia, l the two other diseases. Notwithsta these quantitative variations, no basic ence exists between the bone anomali countered in these three diseases the ences consist only of variations in "freq severity extent and distribution."[9]

COOLEY'S ANEMIA (THALASSEMIA)

Cooley's anemia carries several different names. The term "target cell anemia" is often used because the large erythrocytes of the peripheral blood contain a rounded central area of hemoglobin surrounded by a clear ring.[1] These target cells have also been characterized as "red cells with a nipple," or Mexican hat cells. This disease occurs most frequently among So European peoples, especially in the settlements of Southern Italy and aroun Mediterranean Sea. Hence the design "thalassemia" or "Mediterranean di A benign form of the disease is desig as hereditary leptocytosis,[2] thalassemia or thalassemia trait. This trait may p

as an iron-resistant hypochromic anemia, but in many cases the hemoglobin values are completely normal. The thalassemia trait occurs in some areas 100 times more frequently than the fully developed thalassemia major.

Electrophoresis shows only the presence of normal hemoglobin A and fetal hemoglobin-F, the latter sometimes in quantities up to 90 per cent. However, there is no direct relationship between the amount of fetal hemoglobin and the seriousness of the disease.

Cases of thalassemia reported in America have usually been limited to children of Greek, Italian, Armenian, or Syrian parents. Among the Jews in Palestine, the disease has been found only in the darker skinned Jews, originating from Bucharan near the Caspian Sea and from Kurdistan. The rare cases of thalassemia described in Negro children and the occurrence of the disease in China, Thailand, Burma and Indonesia testify to the migratory tendencies of the Mediterranean peoples.

In thalassemia, characteristic bone changes of the skull can often be observed. The proliferating bone marrow causes rarefaction first in the cancellous part of the calvarium but later in the cortex as well. Due to the rapid proliferation of the erythroblastic elements of the bone marrow, the diploic space expands and the over-all diameter of the calvarium is increased. Both tables are thinned by pressure atrophy, the outer table more than the inner one. Initially, the frontal bones are involved, then the process spreads to the parietal, and finally to the occipital bones. Sometimes the bones of the face and the mandible also increase in diameter. In later stages of the disease, the proliferating bone marrow causes such intense irritation that numerous new bone trabecules develop. These newly formed trabecules run at right angles to the tables of the skull and perforate the outer table, leading to a "hair brush skull." This produces a coarse vertical striation outside the outer table which, in profile roentgenograms, presents as a "hair on end" appearance of the skull (Plate 29*a*). In perpendicular roentgenograms, the skull looks like a sponge with large meshes. This striated appearance of the skull is for all practical purposes typical for the hemolytic anemias. Even when the striated character of the calvarium is excessive, the nasal process and the lower portion of the frontal bone remain free of striation. Although in many instances it seems that the more severe cases of thalassemia are associated with the most extensive changes in the skull, there is no absolute correlation between the clinical severity of the disease and the development of vertical striations.

When clear-cut changes in the skull are present in Cooley's anemia, the long bones also show changes, but the reverse is not always true. In the long bones the marrow cavities are widened and the cortex is thinned and atrophic. The total diameter of the bone increases, leading to fullness of the shaft. The external contours, especially of the short bones, become more rectangular than normal. The distal parts of the long bones, especially of the femurs, are more expanded than the central portions. This expansion of the bone contours may result in a certain similarity with the Erlenmeyer flask deformity, as is frequently seen in Gaucher's disease. The ribs may be broad, lamellation of the inner layers of the cortex of the ribs by the proliferating bone marrow sometimes ensues. The spongiosa is partially destroyed by the proliferating erythroblastic marrow and the marrow cavity is crossed by irregular and distorted trabecules (Plate 29*b*, *c*). These trabecules may be so far separated from each other by the proliferating bone marrow that heavy reticulation of the bone results. Sometimes smaller or larger cystlike spaces can be visualized on the roentgenograms (Plate 30*a*, *b*, *c*). Frequently, there is heavy horizontal striation near the ends of the diaphyses of the long bones. Many of these bone changes already become evident by the end of the first year of life and develop progressively in the growing child. Before puberty

poikilocytosis and increased serum bilirubin with an indirect Van den Bergh reaction. The osmotic resistance of the erythrocytes versus hypotonic salt solutions was significantly decreased. However, the hemoglobin content and number of red cells were normal. In this patient, the normoblastic proliferation of the bone marrow was evidently strong enough to prevent the development of anemia due to the shortened span of life of the spherocytes. Careful roentgen examination of the skeleton revealed increased radiolucency of spine, ribs, pelvis, and clavicles due to the resorption of secondary bone trabecules, with ensuing reticular structure of the cancellous bone and vertical striation of the vertebral bodies. These bone changes were caused by the proliferation of normoblasts and erythroblasts in the axial part of the skeleton where, in the adult, hemopoesis takes place.

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Chapter 19

Bone Lesions in Lymphomatous Diseases (Hodgkin's Disease, Lymphosarcoma and Reticulum Cell Sarcoma)

FREQUENCY

In the different lymphomas—especially in Hodgkin's disease—bone lesions occur more frequently than in the leukemias. Osseous manifestations of Hodgkin's disease can only be visualized on the roentgenograms when the cortex of the bone is involved or when collapse of bone has taken place. As long as the cancellous bone alone is involved, roentgen examination will not reveal any abnormal findings. It follows that a much higher percentage of lymphoma patients with bone involvement will be found at autopsy than by roentgen examination.

In Craver's experience, about 50 per cent of the cases of Hodgkin's disease and 30 per cent of the cases of lymphosarcoma show skeletal involvement at postmortem examination. Steiner[4] reviewed 547 necropsies of Hodgkin's disease with 28 per cent of bone lesions. Falconer and Leonard[1] found at autopsy that 53.3 per cent of their patients had bone lesions, Maxet[4] reports an incidence of 71.4 per cent. In three different series, roentgen examination in vivo revealed skeletal involvement in only 8,[4] 17.8[4] and 15.6 per cent[9] of the patients examined.

ROENTGENOLOGIC FEATURES

It is impossible to distinguish roentgenologically whether skeletal lesions are due to malignant lymphoma or to metastatic malignancies, tuberculosis, myelomas and even giant cell tumors. The diagnosis can be made only if other signs of lymphoma are present, and, in the final analysis, only by biopsy. The cortex of the bone may be either eroded or thickened. If erosion exists, the destructive process has usually progressed from the endosteal side toward the outside, less frequently from extraskeletal lymph node masses towards the bone. Periosteal thickening is commonly present.

It is generally accepted that the bone lesions in Hodgkin's disease are often simultaneously osteolytic and osteoblastic, or even purely osteoblastic.[5,7,10] In lymphosarcoma, far the greater part of the skeletal lesions are allegedly osteolytic in character. Statistically this difference probably exists, but exceptions must be numerous. The experience of Wellens and Jansen,[9] who found osteolytic lesions in 71.5 per cent of their patients with skeletal manifestations of Hodgkin's disease, clearly supports this idea. Furthermore, in occasional cases of lymphosarcoma, osteoblastic deposits have been found, therefore, the osteolytic or osteoblastic character of bone lesions cannot serve for the differential diagnosis between Hodgkin's disease and lymphosarcoma.

The most frequently involved part of the skeleton in Hodgkin's disease is the vertebral column. In this disease the spine is always affected as soon as any other bone shows pathologic changes.[2] Lesions of the spine are especially frequent in the presence of

large paravertebral lymph node masses. This experience points to a direct invasion of the spine by adjacent lymph nodes, which is in contrast to the rarity of such invasion from outward inward in the rest of the skeleton. This may be connected with certain anatomic relations, especially with the drainage of the intraspinal lymph towards the mediastinal and retroperitoneal lymph nodes. It is well known that reversal of the lymph current is a common occurrence, and such a reversal could explain the frequency of Hodgkin's disease of the spine in the presence of paravertebral lymph node masses.

Hodgkin's disease of the spine may be osteolytic (PLATE 31*c*) or osteoblastic in nature (PLATE 31*b*). In the latter case, formation of ivory vertebrae often results. Collapse of the vertebrae affected by Hodgkin's disease readily occurs: in the material of Wellens and Jansen[6] 11 cases of vertebral collapse were noted among 29 cases of spinal involvement by Hodgkin's disease. Even if complete collapse of the vertebrae exists, the intervertebral disk remains nearly always intact. We have encountered only one patient with Hodgkin's disease of the spine in whom the intervertebral space between the two affected vertebrae had been narrowed. Gibbus formation is occasionally observed.

Often the first manifestations of Hodgkin's disease consists of the appearance of small sclerotic areas in pelvis or upper part of the femur. It is difficult to distinguish these areas from bone islands except by serial roentgen photos made at monthly intervals: osteoblastic Hodgkin's lesions gradually increase in size, whereas bone islands do not grow. Thus, extensive osteosclerosis of the pelvis is not rare (PLATE 32). Hodgkin's disease occasionally causes osteosclerosis of the major part of the skeleton.

A lymphoma may cause one (PLATE 31*a*) or multiple sharply delineated osteolytic lesions of the calvarium, which resemble multiple myeloma (PLATE 33*a*, *b*). The differential diagnosis is easy when the lesions perforate through the external table of the calvarium, because in multiple myeloma the palpable tumor is always soft, while in lymphoma it is firm or even hard. Unfortunately, this diagnostic clue is seldom available since, in the majority of cases, neither lymphoma nor myeloma perforate through the calvarium. Needless to say, bone marrow puncture will either prove or disprove the presence of multiple myeloma.

Following intense radiotherapy, reactive changes may occur in the spine in the form of sclerosis of vertebral bodies or intervertebral bone bridges. In such cases it may be difficult to decide whether the anomaly is due to Hodgkin's disease of the bone or to an after-effect of radiation.

CLINICAL FEATURES

Since the spine is so often involved, the first signs of the disease may be neurologic in nature, in the form of radiating root pains, unilateral Babinski reflex or foot clonus. Sometimes patients are admitted with paraplegia, so that only at laminectomy can the correct diagnosis of Hodgkin's disease be made. In this connection it must be mentioned that in about two thirds of the cases of involvement of the cord by Hodgkin's disease, roentgenologic examination of the spine does not show any abnormality. Examination of the spinal fluid, however, nearly always reveals a significant increase in protein.[3]

None of the other parts of the skeleton are immune against lymphomatous infiltration, but there is a predilection for bones rich in red bone marrow: such as pelvis, ribs, sternum and other flat bones.[7] In the long bones, especially femur and humerus, Hodgkin's lesions usually start in the epiphyseal part, and then spread from there into the diaphysis.

When Hodgkin's disease is localized in the sternum,[8] the anterior table is often eroded, and a granulomatous mass may break out

of the sternum. A bulging subcutaneous mass results, occasionally becoming necrotic and ulcerating. This, then, is one of the few occasions where Hodgkin's disease gives rise to an ulcerating lesion.

Clinically, the involvement of the skeleton may present itself as a swelling of the bone, but the most frequent manifestations are pain and tenderness. The "rheumatoid" pains of patients with Hodgkin's disease and lymphosarcoma are often due to bone involvement—even in cases where the roentgenograms do not yet reveal any abnormality. Fever of unknown origin in a patient who simultaneously has a sclerotic lesion somewhere in the skeleton is remarkably often caused by Hodgkin's disease.

There is little value to the rule which states that the presence of bone lesions below the elbow and knee militates against the diagnosis of lymphoma and should indicate, instead, metastases of true malignancies. Too many exceptions invalidate this "rule."

Hypertrophic osteoarthropathy (p. 183) in Hodgkin's disease was described in 1889 by Bamberger from Vienna. Weber[8] and, more recently, Wellens and Jansen[9] have each reported one such case, always in patients who had clear-cut Hodgkin's disease of the lungs.

Some authors are of the opinion that when skeletal lesions can be discovered in lymphoma patients, external lymph node swelling is always present. There are many exceptions to this rule. Several times we have been obliged to resort to bone biopsy in patients with osteosclerotic or osteolytic lymphomatous lesions, because neither lymphadenopathy nor splenomegaly could be found.

In most cases serum calcium and phosphorus are normal. The alkaline phosphatase of the serum is frequently increased. Often it is difficult to decide whether this increase depends upon the osteoblastic activity connected with the formation of the skeletal deposits or upon the liver involvement which so frequently takes place in Hodgkin's disease.

Occasionally a patient with Hodgkin's disease develops severe hypercalcemia due to rapid dissemination of the lesions all through the skeleton. In these cases, all the symptoms and signs of a hypercalcemic syndrome (p. 222) are usually present. Calcium precipitates in the kidneys, resulting in death by uremia. Such acute hypercalcemia only occurs when the Hodgkin's disease is complicated by fever. Fortunately, acute hypercalcemia is a rare occurrence in this disease, and large numbers of Hodgkin patients suffer from prolonged fever without any increase of the serum calcium.

TREATMENT

The pains of the skeletal lesions in lymphoma are often favorably influenced by roentgen treatment. In case the disease has become resistant to x ray radiation, nitrogen mustard treatment may still lead to considerable improvement. This drug is given by intravenous injection of 0.1 milligram/kilogram body weight, to be repeated on four consecutive evenings. An intravenous drip of saline is installed. The drug is dissolved in a small amount of saline and *quickly* injected via the rubber tubing into the intravenous drip. Nitrogen mustard always causes nausea and vomiting. One hour before the injection the patient must therefore receive 2 grains of Amytal orally and 50 milligrams of Thorazine intramuscularly. In some patients who have little tendency to vomiting the treatment can be shortened by administering 0.2 milligram of nitrogen mustard per kilogram body weight on two or even three consecutive evenings.

Nitrogen mustard treatment is followed by leukopenia, which reaches a maximum around the 16th day after the *injection. This is why the treatment* cannot be repeated within two and a half or three months without danger of the development of agranulocytosis.

Nitrogen mustard can also be given by

mouth in the form of T.E.M., or triethylene methylamine. However, it is rather difficult to avoid severe leukopenic reactions or even agranulocytosis during the T.E.M. administration. Unless the patient can be examined daily, the intravenous route of administration seems the safest.

Often the result of nitrogen mustard treatment is surprisingly favorable the fever comes down, the lymph nodes shrink and the bone pains disappear However, relapses always occur and ultimately the patient no longer reacts to the treatment. By that time the lesion may have become x ray sensitive again new roentgen treatment may now suppress the disease. Otherwise, a trial with either Meticorten or ACTH is justified. Sometimes the corticosteroids are able to control the lymphomatous process, at least temporarily By alternating the three methods of treatment mentioned it is occasionally possible to keep the lymphoma patient alive for several years.

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Chapter 20

Skeletal Lesions in Leukemia and Leukemia-Like Conditions

BONE LESIONS IN LEUKEMIA

LEUKEMIA IN CHILDREN AND TEENAGERS is usually acute or subacute, but hardly ever chronic. In this age group leukemia is nearly always lymphoblastic in nature, rarely myeloblastic. Careful roentgen examination reveals the presence of bone changes in nearly all cases of infantile leukemia. Contrariwise, in acute leukemia of the adult skeletal anomalies are relatively rare. The skeleton of children reacts differently than the adult skeleton upon the proliferation of leukemic bone marrow. In children, active bone marrow is present in practically all the bones of the skeleton. In the adult it is concentrated in spine, pelvis, ribs and sternum, whereas the long bones contain mainly fatty marrow. This may well be one of the reasons that leukemia and other diseases of the bone marrow cause more skeletal reactions in children than in adults.

The most frequent roentgenologic manifestation of infantile leukemia is caused by proliferation of leukemic cells below the periosteum of the long bones. This lesion can be visualized on the roentgenograms in the form of an elevation of the periosteum, the space between periosteum and cortex being occupied by leukemic tissue. Very often these subperiosteal changes are most extensive near the joints. Such para-articular involvement of the periosteal space by leukemic infiltration causes tenderness, redness and swelling of joints. Unfortunately these articular manifestations often lead to the erroneous diagnosis of acute arthritis. In a sick child with a so-called rheumatoid arthritis or acute rheumatic fever, resistant to treatment, the possibility of a subacute leukemia must always be considered. Finally, it may be repeated (see p. 89) that comparable pseudoarthritis manifestations are also found in chronic uremia of young patients with para-articular calcinosis.

Another frequent roentgenologic lesion in acute leukemia of childhood consists of a rather extensive bandlike zone of resorption of bone in the region of the metaphysis (PLATE 30*f*). In this area, where under normal conditions rapid ossification takes place, proliferation of leukemic cells is evidently especially intense. On the x rays the metaphyseal areas of extensive destruction of bone trabecules are sometimes sharply defined, but in other cases the osteolytic bands gradually merge with normal cancellous bone (PLATE 30*f*). The metaphyseal lesions are most marked in the neighborhood of the knee joints. This radiologic sign sometimes actually proves the diagnosis of acute leukemia. In childhood the initial stages of acute leukemia may present as an agranulocytosis, a macrocytic anemia or another blood dyscrasia. In such cases the physician may be inclined to cling to the assumption of a drug sensitivity in order to avoid the diagnosis of an incurable acute leukemia. When in such cases, metaphyseal areas of bone resorption appear on the roentgenograms, the diagnosis of acute leukemia is mandatory—all hope must be abandoned. It must be added that in metastasizing neuroblastoma, comparable areas of bone resorption in the metaphysis are encountered which, at least radiologically, cannot be differentiated from leukemic manifestations.

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Chapter 20

Skeletal Lesions in Leukemia and Leukemia-Like Conditions

BONE LESIONS IN LEUKEMIA

Leukemia in children and teenagers is usually acute or subacute, but hardly ever chronic. In this age group leukemia is nearly always lymphoblastic in nature, rarely myeloblastic. Careful roentgen examination reveals the presence of bone changes in nearly all cases of infantile leukemia. Contrariwise, in acute leukemia of the adult skeletal anomalies are relatively rare. The skeleton of children reacts differently than the adult skeleton upon the proliferation of leukemic bone marrow In children, active bone marrow is present in practically all the bones of the skeleton. In the adult it is concentrated in spine, pelvis, ribs and sternum, whereas the long bones contain mainly fatty marrow This may well be one of the reasons that leukemia and other diseases of the bone marrow cause more skeletal reactions in children than in adults.

The most frequent roentgenologic manifestation of infantile leukemia is caused by proliferation of leukemic cells below the periosteum of the long bones. This lesion can be visualized on the roentgenograms in the form of an elevation of the periosteum, the space between periosteum and cortex being occupied by leukemic tissue. Very often these subperiosteal changes are most extensive near the joints. Such para articular involvement of the periosteal space by leukemic infiltration causes tenderness, redness and swelling of joints. Unfortunately these articular manifestations often lead to the erroneous diagnosis of acute arthritis. In a sick child with a so-called rheumatoid arthritis or acute rheumatic fever resistant to treatment, the possibility of a subacute leukemia must always be considered. Finally it may be repeated (see p 89) that comparable pseudoarthritis manifestations are also found in chronic uremia of young patients with para articular calcinosis.

Another frequent roentgenologic lesion in acute leukemia of childhood consists of a rather extensive bandlike zone of resorption of bone in the region of the metaphysis (Plate 30f) In this area, where under normal conditions rapid ossification takes place, proliferation of leukemic cells is evidently especially intense. On the x rays the metaphyseal areas of extensive destruction of bone trabecules are sometimes sharply defined, but in other cases the osteolytic bands gradually merge with normal cancellous bone (Plate 30f) The metaphyseal lesions are most marked in the neighborhood of the knee joints. This radiologic sign sometimes actually proves the diagnosis of acute leukemia. In childhood the initial stages of acute leukemia may present as an agranulocytosis, a macrocytic anemia or another blood dyscrasia. In such cases the physician may be inclined to cling to the assumption of a drug sensitivity in order to avoid the diagnosis of an incurable acute leukemia. When, in such cases, metaphyseal areas of bone resorption appear on the roentgenograms, the diagnosis of acute leukemia is mandatory—all hope must be abandoned. It must be added that in metastasizing neuroblastoma, comparable areas of bone resorption in the metaphysis are encountered which, at least radiologically, cannot be differentiated from leukemic manifestations.

Needless to say in such cases the final differential diagnosis hinges upon careful blood examination, bone marrow puncture, etc. Finally it must be added that in scurvy an area of bone resorption develops in the metaphysis (p 26) However other signs of scurvy are usually sufficiently clear-cut to lead to the correct diagnosis.

Apart from the elevation of the periosteum and the osteolytic zones in the metaphysis, small focal areas of bone absorption are often found (PLATE 30d, e) Rarely, these osteolytic lesions may become confluent and give rise to large cystlike areas, located both in cortex and cancellous bone. Generalized bone resorption all through the skeleton of children with subacute leukemia has been reported in the older literature under the name "osteoporotic or osteomalacic forms of leukemia." Such generalized leukemic bone resorption is decidedly rare.

Acute or subacute leukemia is a fatal disease, regardless of the age group in which it occurs. However in young individuals under the influence of such antifolic substances as aminopterin, 0.5 to 1 milligram daily 6-mercaptopurin, 1 milligram per pound body weight daily alpha methopterin, 2.5 to 5 milligrams daily and others, impressive temporary remissions can be obtained.

This holds true not only for ameliorations of the peripheral blood and the bone marrow smears but for the skeletal lesions as well. Thus, partial reossification of the metaphyseal areas of bone resorption and disappearance of the elevation of the periosteum may occur during the antifolic treatment. Unfortunately such improvement does not last, and—usually after a few months—a terminal exacerbation leads to death.

Skeletal lesions can also occasionally be observed in acute leukemias of adults. The bone anomalies are usually discrete and remain limited to small round areas of bone resorption in and around the neck of the femurs and the scapulae.

In chronic lymphatic leukemia of the adult collapse of vertebrae due to destruction of bone trabecules by the proliferating lymphoblastic tissue will be encountered from time to time. In one case of a very chronic lymphatic leukemia in an older woman we saw widespread osteolytic areas in the terminal phalanges. Still rarer are osteolytic lesions in chronic myeloid leukemia. In these uncommon lesions periosteal proliferation of bone has sometimes been noted. Under these conditions, differential diagnosis between the leukemic lesion and a bone sarcoma or even a neoplastic metastasis may be difficult.[8] In the case of Clements and Kalmon[1] of atypical chronic myelogenous leukemia with osteolytic areas spread through the skeleton, the course of the blood dyscrasia was, to say the least, bizarre. This observation can hardly be used as proof that bone lesions may occur in typical myeloid leukemia.

Special mention must be made of the bone involvement that characterizes the rare and remarkable chloroma. This disease is a myeloid leukemia with tumor formation in which, at biopsy or autopsy the leukemic infiltrations are characterized by a greenish tinge. This green color disappears rapidly mainly under the influence of light. In chloroma, bone destruction is a common finding, especially localized in skull, orbits, spine, ribs and sacrum. This tendency to infiltration of neighboring tissues differentiates chloroma from myeloid or myeloblastic leukemia. Recently we saw an autopsy of a patient with a subacute myeloblastic leukemia with jaundice due to obstruction of the common duct. The latter which is never seen in myeloid leukemia, was caused by the presence of a large mass of myeloblastic tissue with a typical greenish tinge—a true chloroma.

MYELOFIBROSIS AND MYELOSCLEROSIS IN CHRONIC LEUKEMIA

In long standing leukemia of the adult, fibrosis of the diseased bone marrow may occur Osteosclerosis, although decidedly rare, also may develop

Leukemia consists of an abnormal proliferation of the reticulum cells of the bone marrow The overwhelming majority of these proliferating leukemic cells differentiate into immature granulocytes. However, potentially, these abnormal reticulum cells can also develop into other cells, such as erythroblasts, myeloma cells, megakaryocytes, fibroblasts, or even osteoblasts. In some cases of leukemia not all the proliferating reticulum cells dif ferentiate to myeloblasts, but part of the abnormal stem cells mature to fibroblasts. In such cases not only does the bone marrow show the typical changes of leukemia, but, in addition myelofibrosis develops. Myeloscler osis results when the fibrous bundles of the bone marrow calcify

ALEUKEMIC MEGAKARYOCYTIC MYELOSIS OR OSTEOSCLEROTIC ANEMIA

Another condition in which osteosclerosis is combined with leukemia or, at least, with a leukemia like syndrome, has to be distin guished from true myelofibrotic and myelosclerotic leukemia. In the leukemias with myelofibrosis or osteosclerosis, the complete picture of leukemia develops first only in the later stages of the disease does fibrosis or sclerosis of the bone marrow follow In so-called aleukemic megakaryocytic myelosis, often designated osteosclerotic anemia, osteosclerosis and anemia are present initially and only after a long period does the blood pic ture exhibit certain characteristics reminiscent of leukemia. Infiltration of the visceral organs with megakaryocytes—megakaryocytic leukemia—is found at autopsy

As far as is known fifty different names have been suggested to designate this disease.[8] The Boston school objects to the name osteosclerotic anemia, using instead the rather mysterious term agnogenic myeloid meta plasia. Other synonyms are myelophthisic anemia with leuko-erythroblastosis, myelosclerosis with extramedullary myelopoiesis and leuko-erythroblastosis,[10] primary myelofibrosis with myeloid metaplasia and, finally aleu kemic megakaryocytic myelosis, a term which seems to describe the condition correctly

In this disease the anemia is nearly always the presenting sign. In the peripheral blood leukopenia, poikilocytosis, tear drop cells and normoblastosis are frequently encountered. The latter are so prevalent that some of the older clinicians felt justified in naming the disease chronic normoblastosis. In nearly half of the cases megakaryocytes, megakaryocytic nuclei, and often myelocytes can be found in the blood smears. Almost without exception, the spleen—which often reaches the pelvic rim—is greatly increased in size and firm in consistency

In the first stages of the disease, because of the proliferation of new bone trabecules within the marrow cavity the trabecular structure of the cancellous bone is less sharply defined. Roentgenologists customarily report this condition as a so-called "ground glass appearance" of the bones. Later clear cut osteosclerosis appears in different areas of the skeleton (Plate 34*a* *b*) This some times leads to a mottled appearance of the bones. In far advanced cases nearly all the bones are densely sclerotic. Sometimes, sclerosis and/or myelofibrosis (Plate 34*c* *d*) can be found in different parts of the skeleton. Osteosclerosis and osteofibrosis are often present in the same bone, and small osteolytic areas can be visualized within the condensed bone substance. Calcium phosphorus, and

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Chapter 21

Multiple Myeloma

MULTIPLE MYELOMA IS A FATAL DISORDER of the reticuloendothelial system characterized by proliferation of young, abnormal plasma cells, by extensive destruction of the skeletal system and by marked disturbances in protein metabolism.

In 1845 Drs. MacIntyre and Watson observed a 47 year old man with fragile bones and unusual urinary findings. The urine of this patient was examined by Henry Bence Jones,[illegible] who discovered in this specimen the particular protein which still carries his name. This protein, as reported by Bence Jones, dissolved when the acidified urine was heated to boiling. It nowadays still plays an important role in the diagnosis of multiple myeloma, a term first proposed in 1873 by Rustizky a pupil of von Recklinghau Kahler, in 1889, emphasized that the ti of (a) aching bones and pathologic fractu (b) Bence Jones proteinuria, and (c) p gressive cachexia proved the diagnosis myeloma. In the European literature, m tiple myeloma is still frequently referred as Kahler's disease.

The subsequent advent of radiology, he tologic techniques, and biochemical physical methods has considerably broade our diagnostic armamentarium, and it gradually become evident that mult myeloma is a frequently occurring dise Nevertheless, our understanding and tr ment of this complex disease are still p fully inadequate.

ETIOLOGY

The nature and pathogenesis of multiple myeloma remain obscure. Because the myelomatous infiltration of the bone marrow is occasionally associated with the presence of large numbers of plasma cells in the peripheral blood, many authors are of the opinion that myeloma represents the aleukemic form of plasma cell leukemia. In this connection it should be stressed that myeloma differs in certain fundamental aspects from the true leukemic syndromes. The unique disturbances in protein metabolism that are present in myeloma do not occur in leukemias or in any other disease. This holds true for the Bence Jones proteinuria, the characteristic myeloma globulins found at electrophoretic examination and the primary amyloidosis or paramyloidosis which occurs in about 10 per cent of the myeloma patients. Although paramyloidosis is nearly always a manifestation of multiple myeloma [10] paramyloid deposits have also been found in cases wl careful search failed to reveal signs c myelomatous diseases.

BENCE JONES PROTEINURIA

The determination of Bence Jones prc in the urine requires considerable care traces of this remarkable substance be mu

True Bence Jones protein is character by its behavior at different temperature precipitates between 45°C. and 60°C. dissolves again between 90°C and 95°C the following methods are used, Bence J protein will be found in approximately half of the cases of multiple myeloma.

When addition of sulfosalicylic acid s tion to urine does not cause a *precipitate* Bence Jones protein is present. When precipitate, caused by addition of sulfo cylic acid solution dissolves on boiling, presence of Bence Jones *protein is prob*

and the following more precise test of Jacobson and Wilner[29] should be performed.

For the determination of Bence Jones protein only fresh urine should be used. If the protein content of the urine of a myeloma patient is 4+ or even higher, the patient's urine should be diluted with normal fresh urine until the total protein of the mixture has been decreased to 2+. Ten cc. of fresh and adequately diluted myeloma urine are brought to a pH of 5.5 by the addition of a few drops of 2 per cent acetic acid. The pH is checked with nitrazin paper. The urine is then heated in a water bath to approximately 60 C. and held at this temperature for ten minutes. The urine is centrifuged and decanted. The sediment containing the Bence Jones protein is suspended in 10 cc. of normal urine. One drop of concentrated nitric acid is added for every cc. of urine and the specimen is brought to a boil. If Bence Jones protein is present, the solution will clear on heating to 95 C. On cooling, the precipitate will reappear.

For many years it has been known that apart from true Bence Jones protein, other abnormal protein derivatives are frequently encountered in the urine of myeloma patients. Some of these remarkable substances which precipitated at 45°C. to 60°C. but did not dissolve at 95 C., were known as pseudo-Bence Jones proteins. Other proteins, which precipitated at higher temperatures, around 70°C. to 75°C. but did dissolve at 95°C., were designated proteoses. Until recently it was generally accepted that only the presence of true Bence Jones protein actually proved the diagnosis of a myelomatous process. Neither the presence of pseudo-Bence Jones protein nor of a proteose was considered pathognomonic of the disease. All this has changed now that electrophoresis has become the method of choice for the determination of abnormal proteins in serum and urine. This method has become especially popular since simple paper electrophoresis has replaced the original cumbersome electrophoresis machines. It is now recognized that the greater part of the pseudo-Bence Jones proteins and proteoses found in patients with multiple myeloma produce at electrophoretic examination such sharp and tall peaks that they decidedly belong to the myeloma proteins.

Osserman and Lawlor found[30] that in 24 of their 35 patients with myeloma, the sulfosalicylic acid test showed the presence of protein in the urine. In all these cases electrophoretic examination of the urine revealed the presence of myeloma proteins. In 16 of these 24 cases of proteinuria in myeloma the classical reaction for Bence Jones protein was positive. In the 8 remaining cases the latter reaction was negative; nevertheless, electrophoresis revealed the presence of typical myeloma proteins in the urine. The results of the electrophoretic methods clearly demonstrated that proteinuria in a proven case of multiple myeloma is nearly always due to the excretion of Bence Jones protein or of another typical myeloma protein. When sulfosalicylic acid causes a precipitate in the urine of a myeloma patient, negative Bence Jones reactions do not exclude the presence of a myeloma protein. Under these circumstances electrophoretic analysis of the urine is necessary.

This additional knowledge has not diminished the diagnostic significance of true Bence Jones protein. In the presence of this substance the diagnosis of myeloma is certain.

Even in patients with Bence Jones proteinuria who do not show clear-cut clinical signs of renal insufficiency, hyposthenuria, impaired phenolsulfonphthalein excretion and diminished urea clearance bear witness to the damage caused by the passage of Bence Jones protein through the kidneys.

SERUM PROTEINS

As long as only chemical methods were used for the determination of the serum globulin, hyperglobulinemia was found in about 60 per cent of the patients with multiple myeloma. In multiple myeloma, one of the modern modifications of the Howe fraction

ation of the serum often reveals an elevation of the euglobulin fraction or of the pseudoglobulin fraction alone. This differs from the findings in other diseases with hyperglobulinemia (liver cirrhosis, Boeck's sarcoids, Hodgkin's disease, Leishmaniasis, etc.), where both fractions are always elevated. Much more revealing are the results of the electrophoretic examination of myeloma sera. With this method, in order of decreasing frequency, characteristic tall elevations of the gamma, beta or alpha globulin peaks are found. Frequently an abnormal fraction (M protein) migrating between the beta and gamma globulins is present. In this way the presence of abnormal globulins can be elicited in about 80 per cent of the myeloma serum. In 44 of our myeloma patients, alpha patterns were present in 4 cases, beta patterns in 6 and gamma patterns in 21 In 13 patients of this series only minor abnormalities could be observed. If both the serum and urine of myeloma patients are examined electrophoretically, the diagnostic importance of this method becomes still more evident.

For many years it has been known that in the presence of Bence Jones proteinuria the serum globulins are often normal in quantity Exceptions to this rule occur frequently—myeloma patients with Bence Jones proteinuria and hyperglobulinemia are not unusual. When only chemical methods are used for the determination of Bence Jones protein and serum globulins, about 12 per cent of the myeloma patients exhibit neither Bence Jones proteinuria nor hyperglobulinemia. In contrast, electrophoretic methods almost invariably demonstrate characteristic changes of serum and/or urinary proteins in myeloma. Among the 35 cases of multiple myeloma studied by Osserman and Lawlor 17 showed a characteristic electrophoretic abnormality both in serum and urine, 11 in serum only 7 in urine only Therefore, in each case of this series of myeloma patients abnormal proteins could be demonstrated by electrophoresis.[21]

Careful experiments by Hardy and Putnam with labeled carbon and nitrogen must be mentioned. These authors present evidence that Bence Jones protein is synthesized independently and is not a degradation product of the circulating abnormal myeloma globulin.[12,18] The abnormal myeloma serum globulins are most probably glycoproteins in which varying quantities of polysaccharides are conjugated with the protein moiety[14a,20] The abnormal proteins of the myeloma urine do not contain carbohydrate groups.

The increased globulins of the myeloma serum are immunologically different[18] from the globulins found in other diseases with hyperglobulinemia. In addition, the antibody content of the gamma globulin fraction of the myeloma serum decreases progressively in the course of the disease[15] and, ultimately the serum may be completely devoid of antibodies.[16] Then the myeloma patient, notwithstanding the high concentration of abnormal gamma globulin in the serum can for all practical purposes, be compared to a patient with agammaglobulinemia.

PARAMYLOIDOSIS

Amyloid and paramyloid are proteins which contain a small proportion of chondroitin sulfuric acid and other mucopolysaccharides. The localization of paramyloid differs completely from the customary findings in secondary amyloid, which develops after long-standing suppuration, arthritis, syphilis, leprosy and other diseases. Secondary amyloid is found mainly in the liver spleen, kidneys and adrenals.

Sites of predilection for the deposition of paramyloid in myeloma are the joint capsules, producing the clinical manifestations of rheumatoid arthritis the myocardium resulting in congestive failure, the skin manifesting as bizarre, waxy subcutaneous masses and alopecia, the gastrointestinal tract presenting as acute hemorrhages, the tongue causing macroglossia and the larynx causing difficulties in speech and deglutition. In addition, paramyloid may be present in other organs, e.g., lymph nodes and bone marrow In all these organs paramyloid may be found

in the form of hyaline masses. However, the main localization of paramyloid is in the walls of the blood vessels.[32] When paramyloidosis develops in multiple myeloma, Bence Jones proteinuria is nearly always present. At the same time, the globulin content of the serum is often remarkably low

Among the cases of paramyloidosis without myelomatosis, the combination of heart failure and peripheral neuritis deserves special attention.[30a]

THE MYELOMA CELL

Prior to the advent of the routine use of bone marrow aspiration, studies of microscopic sections of bone marrow obtained at autopsy or at biopsy led to the conclusion that multiple myeloma could be caused by rapid proliferation of any of the hematopoietic constituents of the bone marrow (plasma cells, myelocytes, myeloblasts, lymphocytes, etc.) Even multiple myeloma due to rapidly growing erythroblastomas has been described. This concept has completely vanished since bone marrow aspiration by puncture has become popular and bone marrow smears stained with the Giemsa or Wright methods are currently studied. Bayrd,[1] employing this technique, concluded that the myeloma cell invariably was of the plasma cell type. This conclusion has been generally confirmed.[8]

The appearance of the myeloma cell varies from a small, deeply basophilic, almost characteristic plasma cell, to an immature, large, anaplastic plasmoblastic cell, 20-40 micra in diameter The nucleus of the myeloma cell is eccentrically placed, it frequently contains one or two nucleoli, and it lacks the spoked-wheel arrangement of the chromatin network that characterizes the tissue plasma cell. On the contrary the nucleus often presents a closely knit, reticulated appearance, with the chromatin arranged in sausage like clumps. In the younger forms the nucleus is usually vesicular with evenly distributed chromatin, arranged in a fine network. Perinuclear halo formation is common and myeloma cells containing several nuclei are frequently encountered. The large cell type has either a pale or a dark blue cytoplasm, sometimes containing vacuoles or rarely other inclusions. Numerous fine azurophilic granules are occasionally found in the cytoplasm. Larger inclusions, often designated as Russell bodies, are decidedly rare. Vacuoles and nucleoli are lacking in the mature plasma cell type. Cells packed with pale staining vacuoles are referred to as Mott cells.[8] Some myeloma cells are studded with vacuoles containing a deeply staining substance. Occasionally the latter kind of vacuoles extend beyond the outer limits of the cytoplasm. Then, a remarkable cell results which is designated by Stich et al.[44] as a "grape cell."[40]* From their experience the presence of this cell is pathognomonic of multiple myeloma. Large protein crystals can be found in myeloma cells and also in the renal tubular cells of patients with Bence Jones proteinuria.

PATHOLOGY

Multiple myeloma is frequently localized in bones with abundant spongiosa and red marrow such as the sternum, pelvis, spine, calvarium, mandible and ribs. The bone involvement varies from diffuse proliferation of numerous myeloma cells to the formation of large tumor like plasmocytomas. These plasmocytomas often erode through the cortex of the bone and may ultimately present as soft tissue tumors.[5,39]

In most cases of multiple myeloma, both generalized myelomatosis and multiple plasmocytomas are present. Pathologic examination reveals widespread resorption of cancellous bone, destruction of cortical and cancellous bone by grey or hemorrhagic tumor like plasmocytomas associated with multiple fractures and deformities. In some instances a plasmocytoma may produce marked expansion of a bone. Often a large part of an en-

*The frontispiece of "Multiple Myeloma" by Snapper et al.[39] shows an example of a grape cell.

ture bone is completely replaced by tumor tissue. The largest plasmocytomas are found in the pelvis, arising from the iliac wings. Gross destruction of bone may be absent if the proliferation in the medullary cavity remains diffuse. In these cases the autopsy does not reveal the presence of circumscribed tumors and the pathologic findings are limited to a generalized thinning of the cortex and destruction of the secondary bone trabecules. Microscopic examination of the plasmocytomas reveals a strikingly monotonous picture of closely packed plasmoblasts with scanty stroma.

Extramedullary myelomatosis is present in the majority of the cases. This is especially noteworthy in the spleen liver and lymph nodes, where either a diffuse infiltration with myeloma cells and/or discrete nodules of cellular aggregates may be found. Less frequently all other organs almost without exception show some evidence of infiltration. The resulting clinical entities may give rise to considerable differential diagnostic difficulties. The observation of a myelomatous infiltration of a testicle simulating the presence of a primary testis tumor[11] is eloquent proof of such difficulties.

Uremia, a frequent cause of death in multiple myeloma, occurs only when Bence Jones protein is eliminated in the urine. In such cases a so-called myeloma kidney—enlarged, smooth and pale—results. The renal lesion, although not entirely specific, is characterized by extensive plugging of the tubules by large dense eosinophilic casts. The casts, which frequently show calcified and lamellated centers, often extend into the proximal convoluted tubules.[10] This is in contrast to glomerulonephritis, where the cast formation hardly ever affects the proximal tubules. The Bence Jones protein casts are often surrounded by foreign body giant cells. This extensive cast formation has led to the assumption that internal hydronephrosis due to the plugging of the tubules plays an important role in the pathogenesis of the renal insufficiency in myeloma. However extensive cast formation has not been found in every case of uremia in myeloma, associated with Bence Jones proteinuria. Thus, the possibility that Bence Jones protein has a direct nephrotoxic influence must also be considered. Although the glomeruli often appear to be intact at microscopic examination, renal clearance studies have demonstrated that in myeloma kidneys an associated disturbance in glomerular filtration usually exists.

INCIDENCE AND SURVIVAL

Myeloma is usually a disease of later life. Although its onset has been observed—rarely—in young adults, the majority of cases occur between the ages of 40 and 70 Males are somewhat more frequently affected. There is no social or racial predilection. The wide global distribution is well illustrated by the increasing number of cases reported from Japan, where at least 76 cases have been observed.[14] This in all probability does not represent a real increase in incidence, but is rather an indication that local advances in diagnosis have been made which permit earlier recognition of the disease.

Myeloma is invariably fatal, the average duration of life being less than one and-a half to two years after onset of symptoms. Occasionally patients survive for eight or more years, with or without treatment. Recently, Bayrd has reported 4 such cases.[2]

FAMILIAL OCCURRENCE

Occurrence of multiple myeloma in different members of the same family must be a great rarity One instance of a sister and brother who both suffered from myeloma has been reported.[15] The father of these two patients had died from a disease, which also may well have been a multiple myeloma. A sister of the two myeloma patients had a high

sedimentation rate of the red cells and an increase of both alpha and beta globulin fractions.

In view of the close connection which apparently exists between myeloma and primary amyloid, the observations made in the *members of a family with familial amyloidosis* may be of importance.[4] In 5 patients suffering from familial primary amyloidosis, electrophoretic analysis of the serum revealed an atypical peak, situated between the alpha 2 and beta globulin fractions. Later 66 members of the same family were investigated and in 29 persons an atypical electrophoretic pattern in the alpha 2 globulin region was elicited. Thirteen of these 29 persons showed clinical signs of primary amyloidosis. The greater majority of the members of this family with an atypical alpha 2 peak but without any manifestation of amyloid were below the age of 18. In other words, these individuals had hardly reached the age when signs of amyloidosis could be expected. None of the members of this family in whom a normal electrophoretic pattern was found showed any manifestations of amyloidosis. It is of interest that many members of this family also proved to have abnormal serum lipoprotein values.

CLINICAL FEATURES

BONE PAIN

Pain in the bones is the outstanding symptom of multiple myeloma and is present in about 90 per cent of the cases. The onset may be insidious, with vague aches and pains, or it may be explosive—precipitated by a sudden pathologic fracture. As is the usual situation in destructive bone diseases, ultimately the pains become excruciating in character. The pains, which nearly always start in the lower back and ribs, are exacerbated by muscular effort. In the early stages of the disease pain on pressure of the rib cage and limitation of the mobility of the spine can be elicited. Much less frequently the pain starts in other bony structures—hips, legs, shoulders, arms, etc. In the later stages of the disease the pains may be located in almost any part of the skeleton. Severe lancinating pains may also be caused by involvement of nerve roots by vertebral collapse. In the course of the disease the patient gradually becomes a totally incapacitated invalid, crying out with pain at the slightest bodily motion. Occasionally there may be spontaneous pain-free remissions, but this is an unusual occurrence.

Pathologic fractures of one or more bones, predominantly in spine and ribs, occur in about 60 per cent of the patients. The long bones, sternum (PLATE 37*d*) clavicles and pelvis (PLATE 35*a*) may be similarly affected. Pathologic fractures of the sternum are almost pathognomonic of multiple myeloma, at least in areas where osteomalacia does not occur. Fractures in multiple myeloma patients heal rapidly with remarkably good callus formation, but invasion of the callus by myelomatous proliferation always follows. Deformation of the skeleton, especially malformation of the thorax, nearly always results. Severe kyphoscoliosis with shortening of the spine and ribs approaching the rim of the pelvis is a common occurrence in the terminal stages.

TUMOR FORMATION

Soft tissue tumors may present themselves whenever a plasmocytoma has eroded through an underlying bone. Subcutaneous tumors most often (but not exclusively) occur over flat bones (e.g. sternum, ribs, pelvis, mandible, calvarium) and may reach the size of a melon. These subcutaneous plasmocytomas are always soft in consistency. Because of the rich vascular supply such tumors may be hot and pulsatile, and auscultation may reveal the presence of arterial bruits. Occasionally such a perforated plasmocytoma has been erroneously diagnosed as an abscess.

True nodular plasma cell infiltrations of the skin do occur but are relatively uncommon manifestations.[5,30]

PULMONARY INVOLVEMENT

The abnormal antigenicity of the myeloma globulins[33] and especially the absence of antibodies in the abnormal gamma globulin fraction of the myeloma serum (p. 159) are of considerable significance. In the absence of antibodies in the serum a tendency to infections exists. Low grade fever is present in about 40 per cent of the cases of multiple myeloma, while the initial stage may present as a "fever of unknown origin."

The absence of the common antibodies in the abnormal gamma globulin fraction of the myeloma serum, which leaves these patients unprotected against infections,[15,16] is the main cause of the frequency of bronchopneumonia and chronic bronchitis in myeloma. Contributory factors are the deformities of chest and sternum and also the debility of the patient. Finally the sluggishness of the blood flow through the lungs, due to marked increase in blood viscosity and rouleaux formation of the red cells, must facilitate the development of pneumonia. Recurring pneumonitis in adults is always a reason to suspect the possible presence of myeloma.

Both plasmocytomas breaking out of the ribs and paramyloid tumors of the bronchi may be quite large and present on the x ray as a lung neoplasm or a mediastinal tumor. In other cases, plasmocytomas of ribs or sternum infiltrate the subpleural space. The resulting pleural scalloping resembles large pleural tumors and/or metastatic neoplasmas. In rare instances infiltration of the small blood vessels with paramyloid results in bizarre pulmonary infiltrations.[33]

NERVOUS SYSTEM INVOLVEMENT

Proliferation of plasmocytomas frequently leads to collapse of vertebral bodies. When the plasmocytic proliferation penetrates the epidural space, the result is often lancinating pain due to compression of nerve roots and sometimes even transverse lesions of the cord. Among the noninflammatory diseases of the spine producing compression of the cord, only metastatic carcinoma occurs more frequently than myeloma. The cranial cavity can be invaded, with ensuing paralysis of cranial nerves or other cerebral signs. In addition, extensive and disabling neuritic pains may arise from an associated peripheral perineuritis.[8]

RENAL INVOLVEMENT

The marked renal insufficiency which occurs in at least 20 per cent of the multiple myeloma patients is characterized by the absence of hypertension and retinitis. In addition, outspoken edema is a rarity. The combination of azotemia, proteinuria and hyposthenuria, in the absence of hypertension and edema, may serve as the key to the diagnosis. This combination is rare except in myeloma and amyloid. Hematuria is also rarely, if ever, present. The finding of Bence Jones proteinuria proves the presence of a myeloma kidney and excludes renal amyloidosis. On the other hand, extensive edema favors the diagnosis of secondary amyloid. Paramyloid of the kidneys, as frequently observed in multiple myeloma, is hardly ever extensive. Uremia in myeloma, associated with paramyloidosis, is therefore due not to the amyloid, but always to the deleterious action of Bence Jones protein upon the function of the kidneys.

LYMPH NODES LIVER AND SPLEEN

Enlargement of the liver, often considerable, occurs in 40 per cent of the cases. Splenomegaly which usually is less striking, is present in about one fourth of the patients. Generalized slight lymph node enlargement by myelomatous infiltration of lymph nodes is frequently found. In most instances enlargement of liver and spleen is caused by myelomatous infiltration it hardly ever results from replacement by paramyloid. Paramyloid infiltration, however may cause lymph node enlargement.

Treatment with urethane may also cause hepatosplenomegaly (p. 167)

OTHER FINDINGS

Due to the absence of antibodies in the gamma globulin fraction of the serum

meningitis is a rather frequent complication of multiple myeloma.

Paramyloid may lead to many different clinical manifestations. Gastrointestinal hemorrhages, widespread purpura and macroglossia have already been mentioned. In some unexplained cases of heart failure autopsy has shown the presence of paramyloid of the myocardium. Only at this late stage did examination of the bone marrow reveal generalized myelomatosis. Several cases have been published in which primary amyloid of the heart led to the clinical picture of constrictive pericarditis.[11]

ROENTGEN FINDINGS

Roentgen examination reveals that the most frequent sites of myelomatous infiltration are located in the ribs clavicle, sternum, and spine the skull, pelvis and proximal parts of the extremities are also frequently involved. However any part of the skeleton may be affected, and even plasmocytomas of the phalanges have been described.[23,30]

The roentgenographic appearance may vary *from diffuse, generalized, demineralization*" to the presence of extensive, melon-sized tumors with almost total bone destruction. The individual osteolytic lesions are characteristically present as sharply demarcated, punched-out holes, which do not show any evidence of surrounding bony condensation (PLATES 35*a* 36*a* *c* 37*a* *b*) On the other hand, the intramedullary expansion of multiple adjacent plasmocytomas may present a striking "soap bubble" effect, such as is seen in giant cell tumors. When such a lesion is seen in one of the pelvic bones the diagnosis of a plasmocytoma must always be considered (PLATE 35*b*)

The sievelike appearance of the calvarium in myeloma due to an accumulation of innumerable plasmocytomas is well known (PLATE 37*a*, *b*) It should be realized that comparable roentgen pictures may occasionally be *found in multiple metastases of* a malignancy especially mammary cancer (PLATE 46*c*) or in a proliferating lymphoblastoma (PLATE 33*a*) [29] *The differential* diagnosis between these different affections may offer considerable difficulties (PLATE 37*c*) The following experience is sometimes helpful. Lymphoblastoma of the calvarium occasionally breaks out of the skull and forms subcutaneous tumors which are always firm. In contrast, multiple myeloma of the skull only rarely leads to subcutaneous tumors and such subcutaneous myelomas are usually soft.[29]

In vertebral collapse due to multiple myelomas, just as in malignancies, the intervertebral disk usually remains intact, even if the adjacent vertebral bodies are completely collapsed (PLATE 36*a*) [37]

Paravertebral soft tissue densities such as are found in tuberculous spondylitis are hardly ever seen. However exceptions do occur and in rare instances myelomas leading to destruction of the intervertebral disk (PLATE 36*b*) with or without a paravertebral mass have been registered.[15]

Notwithstanding the importance of the roentgen findings for the diagnosis of multiple myeloma, in about five per cent of the cases of this disease no demonstrable roentgen lesions of the skeleton can be elicited.[6,20,31] In such cases a generalized myelomatosis without macroscopic plasmocytomas is present. Until the bone resorption by the generalized myelomatosis has caused the disappearance of 30 to 40 per cent of the bone salts, the roentgenologic signs will be negligible (p 12)

LABORATORY FINDINGS

PERIPHERAL BLOOD

Anemia is present in far the greater part of the patients with multiple myeloma. Critically low hemoglobin values may develop In contrast, rare cases of polycythemia in myelomatous patients have been reported.

Myelophthisis of the bone marrow is perhaps the major cause of the anemia, which may be aggravated by a shortened red cell life span, produced by uremia and hypersplenism. Occasionally an acute hemolytic process with a positive Coombs test is present.

Leukocytosis is present in 20 per cent of the patients, in one half of these cases a shift to the left is noted. Eosinophilia is occasionally seen. While the presence of a small number of plasma cells is noted in the blood smears of about one fifth of the cases, the picture of true plasma cell leukemia is a rare occurrence and is found at most once among every fifty patients with multiple myeloma. Associated with severe anemia, nucleated red cells and immature leukocytes may be seen in the peripheral blood. Such a leuko-erythroblastic blood picture is usually a preterminal event. Thrombocytopenia is found in approximately one fourth of the cases.

A rapid erythrocyte sedimentation rate is present in the majority of cases and is commonly associated with hyperglobulinemia. Marked rouleaux formation and autoagglutination of red cells due to the excess of gamma globulins may be quite striking and may present considerable difficulties in cross-matching unless the matching is done at 28°C.

Myelomatous patients frequently show a marked bleeding tendency. At times this can be attributed to thrombocytopenia, but in the majority of cases the cause remains unknown. In rare instances, skin ecchymoses have been caused by the deposition of paramyloid in small cutaneous blood vessels.

Hemorrhagic tendency may be due to the presence of cryoglobulinemia. Cryoglobulins are globulins which precipitate in the cold and redissolve at 37°C. In cold weather the skin temperature of a patient with cryoglobulinemia decreases far enough to cause precipitation of the cryoglobulin in the surface vessels. This is an additional reason why hemorrhages and superficial necroses easily develop.

BLOOD CHEMISTRY

The serum calcium is increased in more than 50 per cent of the patients with myelomatosis, probably secondary to rapid resorption of bone substance. Values as high as 17 milligrams per cent of calcium have been observed. In contrast to the findings in hyperparathyroidism with bone lesions, the serum phosphorus is normal or elevated. The latter occurs if, as is so frequently the case in multiple myeloma, there is associated renal insufficiency. Then the blood urea nitrogen and creatinine are also increased.

Since the myelomas are purely osteolytic lesions without any osteoblastic proliferation, the level of alkaline phosphatase of the serum remains normal. High alkaline phosphatase is occasionally seen in myeloma patients treated with urethane. This biochemical change is due to the liver damage, which may develop during long standing administration of this drug.

In 2 cases of myeloma an increased alkaline phosphatase content of the serum was found because the function of the proximal convoluted tubules had suffered by the reabsorption of Bence Jones protein. This tubular dysfunction had resulted in a marked increase of the phosphate excretion (p. 45) and the ensuing Lignac Fanconi syndrome had superimposed an osteomalacic condition upon the pre-existing myeloma. The osteomalacia had led to an increase of the alkaline phosphatase of the serum. This combination of diseases must, for the time being, be considered to be a rarity.

The frequent hypercalcemia may cause a so-called hypercalcemic syndrome (p. 222); metastatic calcification is also occasionally present. In one series of 27 myeloma autopsies metastatic calcification was found in ten cases; two patients had renal stones.[7]

The uric acid of the serum is elevated even in the absence of renal failure. This undoubtedly is due to the abnormal proliferation and destruction of the nuclei of the myeloma cells. The hyperuricemia may account for the exceptional cases of gout seen in patients with multiple myeloma.[8]

SOLITARY AND MULTIPLE PLASMOCYTOMAS

The presence of a solitary myeloma should only be considered in the absence of Bence Jones proteinuria, hyperglobulinemia and abnormal plasma cell proliferation in the bone marrow of the rest of the skeleton. The absence of myeloma proteins in urine and serum must be confirmed by electrophoretic examination. Such cases are rare, and in most instances of so-called solitary plasmocytoma (PLATE 35*b*), evidence of generalization of the myelomatosis can be found in the form of one or more of the enumerated abnormalities. Nevertheless, cases are known of solitary plasmocytomas which for many years, sometimes even decades, have remained solitary

Occasionally, patients with multiple plasmocytomas can be found without signs of generalized myelomatosis,[39] but in most cases of solitary or multiple plasmocytoma, generalized myelomatosis either is present or else develops after a relatively short period.

Extramedullary plasmocytomas, which may occur without a bony component, are usually present in the mucous membranes of the respiratory tract and rarely in the gastrointestinal tract. In many instances typical myelomatous dissemination later develops.

DIAGNOSIS

In establishing the diagnosis of multiple myeloma only the presence of Bence Jones proteinuria, myeloma cell proliferation on bone marrow aspiration, and the typical electrophoretic patterns in serum and urine are pathognomonic.

Multiple myeloma may be confused with almost any of the metabolic and neoplastic diseases of bone. It has already been mentioned that the absence of hypophosphatemia and an increase of the alkaline phosphatase of the serum distinguishes myeloma from bone disease due to hyperparathyroidism. In osteomalacia, hypercalcemia does not occur and increase of the alkaline phosphatase is a constant phenomenon. Osteoporosis is excluded by the finding of hyperglobulinemia, Bence Jones proteinuria and/or myeloma cells in the marrow aspirate. The roentgenograms of the vertebral column in multiple myeloma and in postmenopausal osteoporosis may be very similar (PLATE 2*b*) However in the latter disease the resorption of bone is limited to spine, ribs, and pelvis, while in multiple myeloma any other part of the skeleton may also be involved. The presence of bony proliferation, as usually seen in metastatic disease of bone, militates against the diagnosis of multiple myeloma. Nevertheless, considerable confusion with metastatic carcinoma lipoidgranulomas, lymphoblastoma, bone sarcoma and giant cell tumors cannot always be avoided. Ultimately a biopsy will often be required to settle the diagnostic problem.

The presence of renal insufficiency with "heavy proteinuria" in the absence of hypertension should always suggest the presence of multiple myeloma or amyloid disease of the kidney Since uremia in myeloma is nearly constantly associated with the elimination of Bence Jones protein or other myeloma proteins, examination of the urine is usually sufficient to prove or exclude the presence of multiple myeloma. In doubtful cases bone marrow aspiration must be done. Macroglossia or other localizations of paramyloid always warrant a careful search for the presence of multiple myeloma. Gingival biopsy may show the presence of perivascular amyloid infiltrations. Primary amyloidosis without myelomatosis does occur, but is a rarity

In agranulocytosis, Hodgkin's disease, hypersensitivity reactions, lymphopathia venereum and all other diseases of hyperglobulinemia, plasmocytosis of the bone marrow is often present. In these cases the plasma cells are usually mature and lack the characteristics of the myeloma cells described before. Occasionally however, one may be hard put to exclude the diagnosis of multiple

myeloma. Roentgenologic bone survey, determination of serum proteins and a search for Bence Jones protein in the urine will usually serve for the correct diagnosis.

TREATMENT

In the evaluation of any therapeutic regimen for this disease it must be remembered that spontaneous, pain free periods of remission of varying duration occasionally occur. In general, however, the therapy of multiple myeloma gives unsatisfactory results.

RADIATION

Myelomatous tissue is moderately radiosensitive. Thus, palliation may be accomplished by the application of x ray therapy to a large plasmocytoma which has been producing pressure symptoms. In the majority of the cases of generalized myelomatosis the results of x ray treatment are not favorable.

DIAMIDINES

Stilbamidine, pentamidine and later 2 hydroxystilbamidine, have been used in the treatment of multiple myeloma.[34,35] The administration of stilbamidine can effect remarkable relief of pain. However, the duration of the disease process appears unaltered and no clear-cut influence upon the hyperglobulinemia or Bence Jones proteinuria has been observed.

The drug should not be used in patients with Bence Jones proteinuria because it rapidly deteriorates the function of the damaged kidney. Stilbamidine does not harm the normal kidney.

The formation of precipitates in the myeloma cells of patients treated with stilbamidine is a remarkable phenomenon that needs further study. These precipitates contain both stilbamidine and nucleoprotein.

Recently cessation of neuritic pains in multiple myeloma[6] under the influence of 2 hydroxystilbamidine has been reported.

URETHANE

At the present time urethane, a protoplasmic poison and an inhibitor of mitosis, is a popular therapeutic agent. This drug should be administered in the form of 5-grain enteric-coated tablets. The daily dose should vary between 2 and 4 grams. The treatment is continued until a total dose of 200-400 grams has been administered. Thereafter, urethane should be given during alternate months in daily doses of 1 gram. A favorable influence of this treatment is observed in many cases,[36] as is evidenced by abatement of fever and pain and a decrease of the number of myeloma cells in the marrow aspirate. There may be reduction in the serum globulin level and decreased Bence Jones proteinuria, associated with an increase of the serum albumin. Enough urethane should be given to cause leukopenia. The decrease in peripheral white cells should not be allowed to go below 2000 per cubic millimeter.

Unfortunately some of the patients are unable to tolerate this drug because of severe nausea and vomiting. Dangerous side effects, such as thrombopenia and extreme leukopenia, occasionally occur and may preclude a therapeutic trial. Liver damage caused by prolonged urethane treatment has already been mentioned. Although the improvement frequently is only temporary and the span of survival hardly ever increases, a trial with urethane administration should always be recommended.

ACTH AND CORTISONE

ACTH and cortisone may exert a salutary effect upon multiple myeloma. Good results of significant duration are discouragingly rare, and benefit must be mainly attributed to the euphoric side effects of these drugs.

OTHER AGENTS

Radioactive iodine accumulates in myelomatous tissue as it does in many other rapidly proliferating tissues. Administration of I^{131} to patients with multiple myeloma has occasionally exerted a favorable influence upon

the course of the disease. Unfortunately, I^{131} has been without significant effect in many other patients.

When the hypercalcemia rises to 17 milligrams per cent, a calcium poor diet and administration of cortisone and of disodium phosphate in doses of 3 to 5 grams daily is in order

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Chapter 22

Gout

CLINICAL PICTURE

IN THE MAJORITY OF PATIENTS WITH GOUT, the repeated attacks of acute painful swelling and redness of one or more joints involve the first metatarsophalangeal articulation. These attacks of so-called podagra are pathognomonic of the diagnosis of gout. Other joints may also be affected, especially the knee joint (gonagra) and the interphalangeal joints (cheiragra) sometimes the wrist, elbow joint, hips, etc., are also involved. The swelling and redness of the affected joints are often so marked, the pain so excruciating, that a less experienced clinician might be inclined to diagnose an acute inflammation or a phlegmon. Even after the attack has subsided, redness of the affected joint often remains for one or two weeks. Rather frequently acute inflammation of a bursa, especially the subdeltoid bursa, is a gouty manifestation. These acute gout attacks occur nearly exclusively in males. Although females are not completely immune, podagra, gonagra, etc. in women are rarities.

Increase of the uric acid content of the serum is a well-known characteristic of the disease. It is sometimes difficult to evaluate the clinical significance of hyperuricemia. First, it must be noted that in some patients with typical gout attacks the serum uric acid remains normal. On the other hand, there are many diseases which have nothing in common with gout where the uric acid of the serum is increased. This holds true for all diseases where large amounts of cell nuclei are continuously destroyed, e.g. polycythemia, leukemia, multiple myeloma, lymphoblastomas after x ray radiation, etc. In all these conditions gout occasionally occurs, but only as a relatively rare complication. Only patients with polycythemia suffer rather frequently from gout. Finally in all uremic conditions, a high uric acid content of the serum may be found.

The third sign of gout consists of the formation of gouty granulomas, or tophi. In these tophi a central zone of necrotic tissue is present in which large quantities of uric acid and cholesterol crystals are deposited. This central zone is surrounded by layers of inflammatory cells. The lesion is encapsulated in a fibrous tissue envelope.[4] Tophi are found in the subcutaneous tissue, especially in the helix and anthelix of the ears, where they appear as small yellowish nodules. In addition, tophi may be present in the articular cartilages and also within the bone substance. Tophi, hardly without exception, develop only after the gout attacks have lasted for several years. When a subcutaneous tophus is opened with a needle, microscopic examination of the contents reveals the presence of uric acid crystals in the form of long white needles. The presence of uric acid can be further ascertained when the crystalline material is heated in a porcelain dish on a steam bath after addition of one or two drops of nitric acid. After the nitric acid has evaporated a red color results—the so-called murexid reaction.

As long as the tophi remain localized in the ears they have only cosmetic significance. When, however large amounts of uric acid crystals accumulate in or near an articular cartilage or in the large para-articular bursae—subdeltoid, olecranon prepatellar hands, wrists—then deformities may result which may even lead to invalidity. Cases of gout with extensive tophus formation are usually designated as tophaceous gout.

In gout, uric acid precipitates in the lumen and in the wall of the renal tubules, probably because of the increased concentration of the substance in this area. This holds especially true for the gout patients in whom an increased production and an increased urinary excretion of uric acid exist. In the later stages of the disease, uric acid also precipitates in the interstitial tissue of the kidneys. The ensuing renal damage leads ultimately to chronic albuminuria, urinary casts, cylindruria, and azotemia.[3]

The rare fatal termination of gout is nearly always due to uremia.[7] Renal calculi occur in 10 to 15 per cent of gout patients.[8] Such uric acid stones cannot be visualized on a flat plate of the kidneys and thus the diagnosis of uric acid calculosis requires careful examination of the urinary tract with contrast media and wax tipped ureteral catheters.

ROENTGENOLOGIC FEATURES

In the early years of the disease no roentgenologic lesions are present. Even in patients who for years have been suffering from gout, repeated and careful investigation may fail to elicit any radiologic evidence of gout. Gradually a zone of resorption of bone can be visualized in the medial aspect of the bone of the first metatarsophalangeal joint of the podagra sufferers. In this area, a punched-out cystic lesion ultimately develops—the tophaceous change which is typical for gout. Since the original lesion consists mainly of a precipitation and accumulation of radiolucent sodium urate, the tophus in the bone presents on the roentgenogram as a clearly delineated, round, osteolytic area (PLATE 38c) Such tophi are usually adjacent to a joint space and often destroy part of the articular cartilage (PLATE 38a, b d e) When such areas are found in the neighborhood of the first metatarsophalangeal joint, the diagnosis of gout is simple. However tophi can also be found in the skeleton of the hands, knees, wrists, and other bones. When a joint in its entirety has been destroyed and only bone stumps surrounded by a tophaceous mass are left, the roentgen evidence may well be compatible with the presence of a sarcoma. No wonder that under these circumstances, extensive bone resections have occasionally been performed.

Small apparently typical tophi may give rise to confusion. Cystic areas in the neighborhood of joints affected by rheumatoid arthritis may well simulate tophi. Since tophi often break into the joint spaces and cause destruction of cartilage, the roentgenologic differential diagnosis between gout and destructive arthritis may present considerable difficulties. In rheumatoid arthritis, however all interphalangeal joints are affected, in gout, the proximal interphalangeal joints are usually spared. Deposition of calcium in tophi occurs only in severe cases of tophaceous gout of long duration.

A differentiation of tophi from the cystlike digital lesions of Boeck's sarcoids is sometimes necessary When Boeck's sarcoids develop in fingers and toes, the overlying skin and subcutaneous tissue are usually thickened, red, and cyanotic, owing to the presence of chillblain lupus (p. 100) There are often trophic changes of the nails. In Boeck's sarcoidosis the joint space is hardly ever involved. Multiple myeloma also causes round circumscribed osteolytic lesions which, however only rarely affect the skeleton of hands or feet (p 164) In the presence of multiple myeloma, Bence Jones proteinuria and/or hyperglobulinemia will usually be present. A bone marrow puncture will in practically every case, prove or disprove the presence of myelomatosis. On the other hand, both in gout and multiple myeloma, the uric acid content of the serum is increased. The rarity of gout attacks occurring as a complication of multiple myeloma has already been emphasized (p 165)

The differentiation of gout from multiple enchondromas, syphilis, tuberculosis and Paget's disease is usually easy

TREATMENT

Until recently the therapy of gout was limited to a purine-free diet, combined with colchicum preparations and other compounds which by experience cut down the duration of the acute attack. Colchicum has been used for at least eight centuries and is still one of the mainstays of the treatment of gout patients. In recent years cortisone and phenylbutazone have often been found to be helpful. The administration of the latter compound should be limited to a period of not longer than ten days to prevent undesirable side actions. Great progress was made in 1950 when Benemid, or Probenecid, a sulfa-compound, was introduced, which markedly increased the urinary excretion of uric acid.[2,4] This uricosuria results because Benemid inhibits the reabsorption of uric acid from the renal tubules. Ultimately so much uric acid is immobilized that even large tophi may diminish in size, or—still better—disappear.[8] The mobilization of uric acid from the tophi may give rise to a temporary increase of the uric acid content of serum and urine. During Benemid treatment, therefore, the number of gout attacks may increase, and repeated renal colics may ensue. Because of this, it is necessary to combine twice daily one tablet of 0.6 milligram of colchicum to the daily maintenance dose of one or two tablets of 0.5 gram of Benemid.

In cases of moderate damage to the kidneys by gout, this combined treatment may also have a favorable result upon the renal function.[1]

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In gout, uric acid precipitates in the lumen and in the wall of the renal tubules, probably because of the increased concentration of the substance in this area. This holds especially true for the gout patients in whom an increased production and an increased urinary excretion of uric acid exist. In the later stages of the disease, uric acid also precipitates in the interstitial tissue of the kidneys. The ensuing renal damage leads ultimately to chronic albuminuria, urinary casts, cylindruria, and azotemia.[1]

The rare fatal termination of gout is nearly always due to uremia.[7] Renal calculi occur in 10 to 15 per cent of gout patients.[8] Such uric acid stones cannot be visualized on a flat plate of the kidneys and thus the diagnosis of uric acid calculosis requires careful examination of the urinary tract with contrast media and wax tipped ureteral catheters.

ROENTGENOLOGIC FEATURES

In the early years of the disease no roentgenologic lesions are present. Even in patients who for years have been suffering from gout, repeated and careful investigation may fail to elicit any radiologic evidence of gout. Gradually, a zone of resorption of bone can be visualized in the medial aspect of the bone of the first metatarsophalangeal joint of the podagra sufferers. In this area, a punched-out cystic lesion ultimately develops—the tophaceous change which is typical for gout. Since the original lesion consists mainly of a precipitation and accumulation of radiolucent sodium urate, the tophus in the bone presents on the roentgenogram as a clearly delineated, round, osteolytic area (Plate 38c) Such tophi are usually adjacent to a joint space and often destroy part of the articular cartilage (Plate 38a b d e) When such areas are found in the neighborhood of the first metatarsophalangeal joint, the diagnosis of gout is simple. However, tophi can also be found in the skeleton of the hands, knees, wrists, and other bones. When a joint in its entirety has been destroyed and only bone stumps surrounded by a tophaceous mass are left, the roentgen evidence may well be compatible with the presence of a sarcoma. No wonder that under these circumstances, extensive bone resections have occasionally been performed.

Small, apparently typical tophi may give rise to confusion. Cystic areas in the neighborhood of joints affected by rheumatoid arthritis may well simulate tophi. Since tophi often break into the joint spaces and cause destruction of cartilage, the roentgenologic differential diagnosis between gout and destructive arthritis may present considerable difficulties. In rheumatoid arthritis, however, all interphalangeal joints are affected in gout, the proximal interphalangeal joints are usually spared. Deposition of calcium in tophi occurs only in severe cases of tophaceous gout of long duration.

A differentiation of tophi from the cystlike digital lesions of Boeck's sarcoids is sometimes necessary When Boeck's sarcoids develop in fingers and toes, the overlying skin and subcutaneous tissue are usually thickened, red, and cyanotic, owing to the presence of chilblain lupus (p. 100) There are often trophic changes of the nails. In Boeck's sarcoidosis the joint space is hardly ever involved. Multiple myeloma also causes round circumscribed osteolytic lesions which, however only rarely affect the skeleton of hands or feet (p. 164) In the presence of multiple myeloma, Bence Jones proteinuria and/or hyperglobulinemia will usually be present. A bone marrow puncture will, in practically every case, prove or disprove the presence of myelomatosis. On the other hand, both in gout and multiple myeloma, the uric acid content of the serum is increased. The rarity of gout attacks occurring as a complication of multiple myeloma has already been emphasized (p 165)

The differentiation of gout from multiple enchondromas, syphilis, tuberculosis and Paget's disease is usually easy

TREATMENT

Until recently the therapy of gout was limited to a purine-free diet, combined with colchicum preparations and other compounds which by experience cut down the duration of the acute attack. Colchicum has been used for at least eight centuries and is still one of the mainstays of the treatment of gout patients. In recent years cortisone and phenylbutazone have often been found to be helpful. The administration of the latter compound should be limited to a period of not longer than ten days to prevent undesirable side actions. Great progress was made in 1950 when Benemid, or Probenecid, a sulfa-compound, was introduced, which markedly increased the urinary excretion of uric acid.[2,4] This uricosuria results because *Benemid inhibits the reabsorption of uric acid from the renal tubules.* Ultimately so much uric acid is immobilized that even large tophi may diminish in size, or—still better—*disappear.*[8] *The mobilization of uric* acid from the tophi may give rise to a temporary increase of the uric acid content of serum and urine. During Benemid treatment, therefore, the number of gout attacks may increase, and repeated renal colics may ensue. Because of this, it is necessary to *combine twice daily one tablet of 0.6 milli*gram of colchicum to the daily maintenance dose of one or two tablets of 0.5 gram of Benemid.

In cases of moderate damage to the kidneys by gout, this combined treatment may also have a favorable result upon the renal *function.*[1]

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Chapter 23

Gaucher's Disease

GAUCHER WAS OF THE OPINION THAT in the disease that bears his name a primary epithelioma of the spleen existed, and as a matter of fact in the majority of the cases of Gaucher's disease *splenomegaly* is the outstanding sign. The enlargement of the spleen usually starts in childhood and continues unabated through life. Ultimately the spleen may seem to fill the whole abdominal cavity. One Gaucher spleen was found at autopsy to weigh 8 kilograms. In nontropical climates hardly any disease presents splenic enlargement of this size—except aleukemic megakaryocytic myelosis, chronic myeloid leukemia and, occasionally, Hodgkin's disease.* On the other hand, exceptional cases of Gaucher's disease are encountered where the spleen can be palpated only with difficulty. The liver is nearly always enlarged, but less so than the spleen. Recently we saw a patient with extensive bone lesions caused by Gaucher's disease in whom both palpation and roentgen examination failed to reveal any enlargement of spleen or liver.

With few exceptions the peripheral lymph nodes are not enlarged. In contrast, the visceral lymph nodes are often enlarged and colored brown by the accumulation of pigment.

The skin is frequently brown and pigmented, often more over the legs than over the rest of the body. Pigmentation of the mucous membranes can hardly ever be elicited. A wedge-shaped, brownish thickening of the subconjunctival tissue, designated pinguecula, is often present. The base of the wedge lies along the cornea, the apex of the triangle near the inner angle of the eye. This pinguecula is frequently seen in older persons, but is a rarity in childhood. As in all cases of splenomegaly anemia, leukopenia and thrombopenia commonly occur in Gaucher's disease. The latter anomaly is responsible for the hemorrhagic tendency from which patients with Gaucher's disease occasionally suffer.

Histologic investigation reveals that the hepatosplenomegaly and the visceral lymph node swelling are due to the proliferation of a very large cell which was first described by Gaucher. It is now recognized that the Gaucher cell represents a reticulum cell which is filled with kerasin, a specific lipoid. This lipoid contains nitrogen but no phosphorus and is therefore chemically different from both cholesterol and lecithin, these being the other lipoids which may accumulate within reticulum cells, causing xanthomatosis and Niemann-Pick's disease, respectively.

The Gaucher cells, measuring 20 to 80 microns, have a small pyknotic nucleus. Often binucleated Gaucher cells are found. The cytoplasm, which hardly stains with Wright or Giemsa, shows a characteristic wrinkling. These Gaucher cells are mainly derived from the adventitial cells of the small blood vessels. They occur not only in liver, spleen and lymph nodes, but also in the bone marrow. A bone marrow puncture is usually sufficient to make the diagnosis of Gaucher's disease; a splenic puncture is hardly ever necessary.

In the bone marrow smears the large cells with their small pyknotic nuclei and clear unstained, wrinkled cytoplasm can easily be recognized between the normal bone marrow elements. The displacement of the normal cells of the bone marrow by the proliferation of these abnormal elements partly ex

plains the anemia, which is a fairly constant sign of Gaucher's disease. In addition, hypersplenism, caused by the enlarged spleen, also contributes to the anemia. Occasionally, reticulocytosis of the peripheral blood, increase of the indirect bilirubin of the serum and perhaps even a positive Coombs test are proof of the hemolytic character of the anemia.

In the liver the Gaucher cells proliferate in the portal triads and in the sinusoids. Often some increase of the fibrous tissue of the portal spaces is found. Nevertheless, development of a genuine liver cirrhosis is decidedly uncommon in this disease,[9] and only a small number of such cases has been described. Recently a new report of Gaucher's disease with cirrhosis of the liver and ascites has been published.[7] In this case a massive accumulation of Gaucher cells was found in the posterior lobe of the pituitary, the infundibulum and the hypothalamus.[7] Theilum,[8] who first reported this finding, believes that close relationships exist between the microglia of the pituitary area and reticulum cells.

The tendency to localize in and around the pituitary gland sheds light upon the rapid and malignant course of Gaucher's disease in infants. Here the symptoms and signs are mainly cerebral in nature. At autopsy extensive damage of the small and large pyramidal cells is prevalent. Gaucher's disease in infants is usually fatal within a few months, which is in sharp contrast to the benign course of the disease in older children and in adults, where it usually extends over many decades without compromising the general condition. In the stormy infantile cases, accumulations of Gaucher cells may be found not only in the liver spleen, bone marrow and lymph nodes, but also in other visceral organs.

The disease is familial and hereditary. As a rule, only the members of one generation are affected, although the occurrence of Gaucher's disease in two or three generations has occasionally been observed.

Special mention must be made of the extensive bone lesions, which are the result of the infiltration of the bone marrow by Gaucher cells. The proliferating Gaucher cells destroy the trabecular structure of the cancellous bone, from which a motheaten appearance of the involved skeletal part ensues. The cortex of the bone is also thinned and even eroded by the onslaught of the Gaucher cells. In the later stages of the disease partial sclerosis of the Gaucher lesions is sometimes present, manifesting itself as mottling of the bone.[11] Moreover, formation of new bone may take place within the medullary cavity of the Gaucher bone. This is considered to be due to secondary calcification of collagenous fibers in old Gaucher lesions.

The proliferation of the kerasin-laden histiocytes often causes an increase of the diameter of the bone (PLATE 39). This swelling of the bone is most marked in the distal part of the femur, which leads to a bottle- or club-shaped deformity of the metaphyseal area. The latter abnormality is usually referred to as an Erlenmeyer flask appearance of the femur.

The same proliferation of Gaucher cells also debilitates the neck of the femur. As a secondary effect, aseptic or avascular necrosis, allegedly due to embolization of blood vessels by Gaucher cells, results. Under the influence of mechanical stresses and weight bearing, this leads to partial collapse of the femur neck (PLATE 40a) and resorption of the acetabular bone. Finally, the x ray picture of the deformity of the femoral head may resemble a severe form of osteoarthritis.[1,8]

In younger persons the avascular necrosis leads to bilateral coxa vara, *mushrooming* of the femur heads and widening and shortening of the femoral necks.[3] In such patients Gaucher's disease presents as Legg Perthes' disease or osteochondritis juvenilis deformans.[3] There is however one difference: in Legg Perthes' disease the epiphyseal growth nucleus is normal before the osteo-

chondritis begins. In Gaucher's disease—as far as is known—the epiphyseal center is never completely normal.[4] Comparable lesions are sometimes present in the neck and head of the humerus, in the pelvis and in the spine. Gaucher patients with widening of the lumbar intervertebral disks and partial collapse of vertebrae are occasionally observed (PLATE 1b) in whom the condition is usually diagnosed as osteoporosis. In such cases of outstanding decalcification of the spine due to Gaucher's disease, widespread bone resorption outside the axial skeleton can always be observed.

One of our cases of Gaucher's disease without hepato- or splenomegaly was originally diagnosed because of the decalcification as postmenopausal osteoporosis of the spine (PLATE 1b) However, in addition, generalized bone resorption was present in humeri (PLATE 40b) and femora and especially in the skeleton of the hands (PLATE 40c) No so-called typical lesions such as Erlenmeyer flasklike swelling of the supracondylar area of the femur or deformity of femur or humerus head were present. The diagnosis became evident when a sternal marrow puncture was done. A few examples of Gaucher's disease limited to the skeleton and without clinical evidence of enlargement of liver and spleen have been reported.[9]

The blood chemical findings in general are normal. Recently, Tuchman et al. have pointed out that in this disease an increase of the acid phosphatase regularly occurs.[10]

Splenectomy is sometimes indicated to relieve the mechanical discomfort caused by the tremendously enlarged organ. The anemia, if proven to be hemolytic, may also require a splenectomy Splenectomy should be avoided in the childhood form of this disease, because in this age group the skeletal lesions tend to become rapidly progressive following removal of this organ.

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Chapter 24

Osteopetrosis, Albers-Schonberg's Disease, Marble Bone Disease

CLINICAL FEATURES

IN OSTEOPETROSIS THE NORMAL GRACEFUL structure of cortical and cancellous bone is replaced by excessively dense structureless bone, apparently abnormally rich in calcium salts. The disease is always symmetric. Notwithstanding the excessive radiopacity of the skeleton, fractures of the bones readily occur, even after apparently insignificant traumas, hence the synonym "osteosclerosis fragilis generalisata."

In children the presence of osteopetrosis is much more serious than in adults. The most dangerous form already starts during the development of the fetus in utero.[1] Fortunately this form of the disease occurs only rarely. Such children, born with hydrocephalus, compression of cranial nerves especially optic and acoustic nerves and marked anemia, die shortly after birth. When the signs of the disease are discovered within the first year after birth, the span of life hardly ever exceeds puberty. In such cases mental, neuromuscular and skeletal development is usually retarded, nystagmus and compression of the cranial nerves is present,[6] decay of teeth is excessive, and osteomyelitis, especially of the jaw and pathologic fractures with ensuing deformities easily occur. Often hepatosplenomegaly develops together with anemia, leukemoid or even true leukemic blood changes.

In sharp contrast to these dangerous forms of the disease in children, the course of osteopetrosis in adults is benign.[7] The adults with osteopetrosis do not show any symptoms or signs of the disease during childhood or adolescence. In such cases the osteopetrosis is usually discovered by chance when the adult patient is examined roentgenologically for an ailment not connected with the skeletal system. Less frequently the occurrence of multiple fractures after insignificant trauma is the immediate cause for roentgenographic examination of the skeleton.

In about half the cases of osteopetrosis familial traits can be demonstrated.[2,4,9] It should be noted, however, that the fulminant cases of osteopetrosis in newborns are usually sporadic in nature.[7] From the study of families with adult osteopetrosis it appears that the disease follows a recessive Mendelian trait because, in general, it attacks different siblings of one generation only. Nevertheless, the usual exceptions to this rule occur and adult forms of the disease where more than one generation of a family is involved have been reported.

The severe anemia, hepatosplenomegaly, compression of cranial nerves, disappearance of the medullary cavity and retardation of development which are so frequent among children with osteopetrosis are very rare in the adult form. In fact, most authors agree that half the adult forms of osteopetrosis are asymptomatic except for the tendency to pathologic fractures which exist in about one third of the adult cases. The bones break like "sticks of chalk,"[10] which must be responsible for the transverse character of the fractures. The latter heal only slowly and frequently leave deformities. Serum calcium and phosphorus are normal and the alkaline phosphatase of the serum is hardly ever in-

creased. There is one report indicating that the acid phosphatase in the serum of children with marble bone disease is increased.[11] Notwithstanding the difference in severity between the infantile and the adult forms of the disease, the nature of the bone changes as elicited on the roentgenograms is fundamentally the same.

ROENTGENOLOGIC FEATURES

The outstanding feature is the bilateral symmetrical increase in density of the bone with loss of the trabecular pattern. The marrow cavity has either completely or nearly completely disappeared (PLATE 41*a*) Often the films have the appearance of under exposed photographs. In the uniformly dense shafts and especially in the metaphyses of the long bones, a vertical, coarse striation can be visualized which leads to a so-called "celery" appearance of the bone. These vertical striations are best visualized on over penetrated exposures. The metaphyseal parts of the long bones are expanded—so-called "clubbing of bones." This clubbing, which often ends abruptly at the junction of metaphysis and diaphysis (PLATE 41*a* *c*), may affect only parts of the skeleton. It is sometimes limited to the distal ends of the femurs and the proximal ends of the humeri. In order to explain the prevalence of the clubbing in such parts of the skeleton, it has been pointed out that these are the most rapidly growing metaphyses of the body Whether or not this explanation is correct remains to be seen. This theory certainly cannot be used to explain the clubbing of the posterior clinoid process of the sella turcica which is present in practically all cases of osteopetrosis (PLATE 41*b*)

In the pelvis, which apparently is always affected by osteopetrosis, concentric rings of alternating increased and decreased density are usually present (PLATE 43) Much rarer are spokes of dense bone substance which fan out in radial directions.

In the skull, the base and especially the sella turcica are sclerotic (PLATE 41*b*) The thickening and clubbing of the clinoid processes have already been mentioned. In other cases the skull in *its entirety* may be affected by osteopetrosis here the calvarium is abnormally thick and sclerotic, resulting in a so-called "porcelain skull" (PLATE 42*a*) where the paranasal sinuses have disappeared and the frontal and nasal bones are thickened. Narrowing of different cranial foramina can usually be demonstrated.

In many adult patients with osteopetrosis the complete picture, as sketched above, is not present. The lesions in such cases may be limited to bands of alternating densities situated in the metaphyses.[8] In other cases the marrow cavity has been spared and the abnormal structure may only present as an abnormally thick bulky cortex (PLATE 42 *b* *c*) The bones of the hands and feet are usually involved.

In the spinal column dense plates of bone are present, paralleling the superior and inferior terminal plates of the vertebral body The middle third of the vertebra, however is normal in density Thus, the formation of a so-called "sandwich vertebra" results (PLATE 43) The spinal and the transverse processes of the vertebrae are hardly ever involved.

In contrast to the experience of certain authors, the clavicle and the mandible are also frequently affected. A highly interesting and important point has been brought out by Henkel and Beiler[7] In the carpal and tarsal bones a central block of normal bone is often present, surrounded by the abnormal marble bone, a picture which is usually designated as "bone within bone." The sclerotic part of bone in its turn is surrounded by an external layer of normal bone. In such cases the nucleus of normal bone represents the size the bone had reached before the osteopetrosis started. The dimensions and the shape of the normal bone permit determination of the patient's age at the onset of the disease.

The external layer of normal bone has been laid down between the time the osteopetrosis became dormant and the bone growth was completed. The total size of the sclerotic part of the bone with its normal nucleus indicates at what age spontaneous healing of the osteopetrosis occurred.

Analogous calculations can be made when within the marble bone epiphyses of the long bones inclusions of normal bone can be visualized. Here again, the latter inclusions represent the size the epiphyseal centers had reached at the beginning of the development of the osteopetrosis. Henkel and Beile present roentgenograms of a calcaneus where the inclusion of normal density measured 34 millimeters in transverse diameter. They concluded that the disease must have started when the patient was three years of age. The outer layer of normal bone indicated that the osteopetrosis must have become inactive during early adolescence. Such measurements lead to the impression that even the adult form of osteopetrosis always starts in early childhood or even before.

BLOOD PICTURE

The formation of "sandwich vertebrae" may at least partly explain why in the adult form no anemia is present. Even if the terminal plates of the vertebrae are markedly thickened, there is still a narrow medullary cavity left where hematopoiesis can take place. In the infantile form of osteopetrosis the whole vertebral body is transformed to one block of marble bone. It is true that in the adult form, as in the childhood cases, the long bones are sometimes completely sclerotic. Nevertheless, even in the extremities the cancellous bone is less compromised in the adults than in children with osteoporosis. In addition, in contrast to childhood, in adult life by far the greater part of the bone marrow of the long bones is fatty. The adult evidently depends for his blood formation mainly upon the bone marrow of the axial skeleton. Therefore, even if only part of the marrow cavity of the vertebrae is saved, hematopoiesis of the adult patient may remain normal. Finally it is nowadays believed that the anemia of children with osteopetrosis not only depends upon the disappearance of the bone marrow cavity but is at least partly due to a complicating myelofibrosis.[4] Adults with osteopetrosis evidently have less tendency to develop myelofibrosis than children. In addition, the presence of hemolytic anemia in children with osteopetrosis has also been ascertained.[4]

CHEMICAL AND PATHOLOGIC DATA

Until recently our knowledge of the chemical and pathologic characteristics of the bone in osteopetrosis was limited to the data obtained at the autopsy of young children who had died from this disease. In the infantile osteopetrotic bone, the bone ash, which under normal conditions varies between 55 and 67 per cent of the total weight, was increased to 67 to 72 per cent. Histologically the density of the staining of the abnormally broad cement lines is one of the outstanding features. This finding seems to indicate that the normal osteoclastic resorption of bone matrix is decreased. A scarcity of the collagen fibrils is also reported, which could explain the fragility of the bones.

In 1954 Enticknap[8] published the results of the autopsy of a woman of 41 years of age in whom a completely asymptomatic osteopetrosis had been found. She had never suffered any fracture. The cause of death was rupture of an aneurysm of the circle of Willis. The intensity of the osteopetrosis was well illustrated by the enormously thick and heavy calvarium. The diploë had completely disappeared. The calvarium weighed 1208 grams as compared to a normal weight of 302 grams. Nevertheless, none of the foramina of the skull was narrowed. The cortex of all the long bones was thickened

the mean thickness of the cortex of the middle of the humerus was 7 millimeters, of the femur 1.0 centimeter. The trabecules of the cancellous bone were coarse.

It is highly interesting that calcium 25.3 to 26.3 per cent, phosphorus (as PO_4) 34.2 to 35.0 per cent, carbonate content (as CO_3) 4.3 to 4.9 per cent of dry osteopetrotic bone, were all within normal limits. The content of both collagen, 23.4 to 24.9 per cent, and hydroxyproline, the characteristic amino acid of collagen—3.13 per cent of dry bone—were also normal. The question could be raised whether these normal figures will also be found in adult patients with osteopetrosis and a tendency to pathologic fractures. Even so, the normal chemical constitution of this very abnormal adult marble bone is certainly noteworthy.

Careful experiments revealed that the skull was harder than normal and that it bent and broke more easily whereas the long bones were softer than the skull, more resilient and more resistant to fractures.

The haversian canals of the osteopetrotic bones were smaller than normal and, consequently, the specific gravities of the skull (1.72), the tibia (1.94), and the femur (2.16), were higher than the normal specific gravity of the tibia (1.46).

PATHOGENESIS

Most authors are of the opinion that the pathogenesis of osteopetrosis is closely connected with insufficient osteoclastic resorption of the primary bone trabecules which are formed within the metaphysis during the closure of the epiphyseal disks.[7] These primary chondro-osseous trabecules result from the calcification of the original columns of cartilage. Since the latter columns run parallel with the vertical axis of the bone, the primary spongiosa is also vertically oriented. Under normal conditions these primary bone trabecules are resorbed by osteoclastic action and replaced by new trabecules whose arrangement and orientation depend upon the influence of the stresses and strains to which the skeleton is continuously exposed. The resulting structure of the cancellous bone is responsible for the resilience of the skeleton and its resistance against traumatic influences. It is believed that the absence of absorption of the original bone trabecules explains why a vertical striation can be visualized on the x rays of the metaphyses of patients with osteopetrosis. These vertical radiopaque stripes allegedly represent the abnormally thickened, nonabsorbed primary chondro-osseous trabecules. The insufficient osteoclastic activity could also explain why large islands of original cartilage are always found in osteopetrotic bone. At the same time, the cement lines of the bones are abnormally thick and dense, because along the cement lines of patients with osteopetrosis only bone deposition, and not bone resorption, takes place. A lack of osteoclastic bone resorption without excessive bone formation would explain why in osteopetrosis no striking hyperfunction of osteoblasts exists. This must be the reason that in this disease the alkaline phosphatase of the serum is not increased.

Osteoclastic bone resorption of the primary bone trabecules starts only when the child is 8 months old. In other words, during the first 8 months of life the absence of osteoclastic destruction of bone substance leads to a physiologic osteopetrosis. Thus, it could be reasoned that when the osteoclastic bone absorption remains minimal even after the age of 8 months has been reached, osteopetrosis must ensue. Unfortunately present day findings indicate that the pathogenesis of osteopetrosis cannot be explained by decreased osteoclastic bone resorption alone. Enticknap mentioned that in the bone obtained at the autopsy of his patient with osteopetrosis both osteoblastic and *osteoclastic* activity were found to be within normal limits.[8] The same conclusion was reached by Engfeldt and associates, who

examined the bones of two children with osteopetrosis using modern biophysical methods.[3]

The arrangement of the collagen fibers examined with polarized light is quite abnormal, thus explaining at least one of the causes of the abnormal fragility of the bone in osteopetrosis. Wide angle x ray diffraction shows that the microcrystalline structure of the bone salts is the same as in normal bone. Routine chemical analysis makes it clear that the ratio of calcium to phosphorus in osteopetrosis is the same as in normal bone. This confirms the general opinion that osteopetrosis is not the result of an abnormality of the calcium metabolism. The Swedish scientists demonstrated by microradiography that in the abnormal bone, filling up the marrow spaces, both excessive calcification and intense bone resorption were going on.

Since typical areas of bone resorption can be demonstrated, an inhibition of osteoclastic bone resorption cannot be the only cause of osteopetrosis.[4,5] This does away with most of the current explanations of the pathogenesis of the disease. The Swedish investigators conclude from their microradiographic studies that the normal bone resorbed by osteoclastic activity is replaced by immature bone which never develops to maturity. The replacement of this immature bone is then inhibited.

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Chapter 25

Neurofibromatosis of Bone

IN 1882 RECKLINGHAUSEN DESCRIBED THE histology of congenital neurofibromatosis. He made it understood that the characteristics of the disease include the presence of tumors, taking issue from the nerve sheaths, both of the cranial and the peripheral nerves. Soft fibromas (mollusca fibrosa) of the skin and pigmented cutaneous areas are almost always present. The soft fibromas may be few or they may number several thousand. They may be sessile, slightly raised or pedunculated. Their size may vary between a rice granule and a small melon. Large blotches of brown pigment or café au lait spots, present at birth or developing during infancy are among the most constant features of the disease. The pigmented areas usually increase in size during the growth of the patient. The classical contention that in neurofibromatosis the patches of pigment have smooth edges has been generally confirmed. In contrast, the edges of the brown spots in polyostotic fibrous dysplasia are serrated in character (p. 132)

A certain amount of confusion in nomenclature has arisen because Recklinghausen described not only neurofibromatosis but also generalized osteitis fibrosa cystica. In both diseases, to which Recklinghausen's name is attached, the roentgenograms may reveal cystlike areas. The presence of such areas in two diseases, completely different in nature, has sometimes erroneously led to the assumption of a close etiologic relationship However Recklinghausen's bone disease is the result of hyperparathyroidism, whereas neurofibromatosis (Recklinghausen) is a completely different entity

Structural changes of the vertebrae result from the development of a neurofibroma of the intervertebral ganglia. Enlargement of the intervertebral foramina with or without compression of vertebral bodies may then follow Because part of the neurofibroma of the intervertebral ganglion is situated within the vertebral canal, partly outside of the spine, the resulting picture has been designated as a "dumbbell tumor" In this condition, root pains are almost always present. Ultimately a paraplegia may ensue which requires operation within the first hours after the paraplegic syndrome has developed. PLATE 44*d* shows the destruction of bone caused by a neurofibroma of the sacrum. Finally it may be mentioned that so-called acoustic nerve tumors are usually neurofibromatous in nature.

Of special importance are the frequently described cystlike osteolytic changes of the skeleton in neurofibromatosis.[8] These osteolytic areas are actually caused by invasion of the bone by a neurofibroma. As a rule, the neurofibromas of the bones have the appearance of bone cysts in the anteroposterior view only[1] The lateral view proves that the cystlike appearance is caused by a lesion which penetrates into the bone from the outside. The osteolytic lesion is evidently due to the presence of a subperiosteal neurofibroma, which causes smooth erosion of the cortex by pressure and thereby extends into the bone at the site where the nerve enters the bone.[1] True central neurofibromas may actually seem to develop within the cancellous part of the long bones, especially the femur and the upper end of the tibia. The rest of the skeleton may also be involved. Fairbank is of the opinion that in such cases the neurofibroma first causes atrophy of the cortex by pressure.[3] Thereafter the adjacent periosteum generates a thin shell of bone which covers the neurofibroma. In his

opinion, therefore, such apparently endosteal cystic lesions also are actually cortical in nature. Sometimes a large plexiform neuroma develops which can be palpated as a broad based subcutaneous mass. In such cases adjacent bone lesions are nearly always present. All neurofibromas show a tendency to sarcomatous degeneration, especially the large plexiform neurofibromas of the extremities.

In neurofibromatosis congenital bone lesions also occur.[3] About 40 per cent of all cases of neurofibromatosis show kyphoscoliotic changes of the spine. This deformity usually starts in the lower dorsal spine but it may also initiate in the cervical spine. The kyphoscoliosis is nearly always progressive. Numerous examples of neurofibromatosis combined with congenital pseudoarthrosis, especially of fibula and tibia, local gigantism, elephantiasis, infantilism, and developmental anomalies of the cervical vertebrae have been reported. Part of the long bones of patients with neurofibromatosis may be curiously slender. Mondor and Léger described a patient with exceedingly thin shafts of humerus, ulna, and radius and contrasting markedly bulbous condyles.[5] The skull cap may show sclerotic tables. In short, in neurofibromatosis, congenital anomalies of the skeleton abound.

The combination of neurofibromatosis with osteomalacia—first described by Gould in 1918[6]—has been frequently reported by other authors. Recently this problem has been discussed anew by Swann,[7] who described 5 cases of neurofibromatosis with widespread resorption of bone and Milkman's fissures. In all these patients a disorder of the renal tubules, a so-called tubular dysfunction caused by Fanconi and Girardet's[8] phosphate diabetes, was present (p. 44). It may be repeated that in this condition the tubular reabsorption of phosphorus is impaired, resulting in marked phosphaturia and low serum phosphorus. At the same time, the urinary calcium excretion falls far below normal because an excess of calcium is excreted into the intestine. The losses of phosphate lead to insufficient calcification of osteoid, i.e., to osteomalacia. In the cases of Recklinghausen's neurofibromatosis complicated by osteomalacia, no other causes for osteomalacia were found. Steatorrhea, lack of vitamin D and renal tubular acidosis have all been excluded. All patients had a low serum phosphorus, excessive phosphaturia and abnormally high intestinal calcium excretion. Evidently, this tubular dysfunction is one of the congenital hereditary anomalies which so often are associated with neurofibromatosis.

Administration of moderate doses of vitamin D to patients with this phosphate diabetes is ineffective. However, both in children and in adults this syndrome of so-called "vitamin D-resistant rickets" is favorably influenced by the administration of massive doses of vitamin D, e.g., 200 000 to 500,000 international units daily combined with a high calcium intake (p. 45).

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Chapter 26

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy, first described by Marie in 1890 is a symmetric, painful swelling of the ends of the long bones, combined with a soft, edematous infiltration of skin and subcutis. Roentgen examination reveals an increase of the size of the bone due to the presence of an ossifying periostitis. This hypertrophic osteoarthropathy is most marked in the bones of forearms and legs, less intense in humeri and femurs. The metacarpals and the metatarsals and, in extensive cases, occasionally even the flat bones may participate in the disease. Sometimes the joints are swollen because the inflammation of the synovia, together with nonspecific changes of the articular cartilage, lead to an intra-articular exudate. In exceptional cases a dorsal kyphosis develops.[a] Clubbing of fingers is practically always present.

Rarely has hypertrophic osteoarthropathy been observed to precede the development of clubbing of the fingers. The latter consists only of swelling of the soft tissues of the fingertips without any marked alteration of the bone of the distal phalanges. Clubbing of fingers can be considered to be the initial stage, while hypertrophic osteoarthropathy is the final stage of the syndrome.

The intensity of the bone pains varies from case to case. Although they may often be relieved by aspirin and thus be of only minor importance, some patients complain bitterly of deep-seated burning pains which are not relieved by narcotics. In the severest cases the distal ends of the extremities involved present a cylindrical swelling due to a firm and localized edema. The joints are practically immobilized, and when the extremities are in a dependent position the pains may become intolerable. Even in cases where the primary disease is fatal in character, the discomfort caused by the hypertrophic osteoarthropathy may be the outstanding complaint.

In cases where the periosteal and joint pains precede the clinical symptoms and signs of the underlying disease, the patients may be treated for a considerable time for "rheumatoid arthritis" before the correct diagnosis is made.

ROENTGENOLOGIC FEATURES

New formation of subperiosteal bone due to chronic proliferative periostitis is most frequently found in the tibia,[a] radius, ulna, femur humerus, metacarpals and metatarsals. The subperiosteal densities represent newly formed, vascular porous bone deposits, most marked along the distal epiphyses of the long bones and at the sites of the musculotendinous insertions (Plate 44a) Ultimately, the ensuing neocortex, 1 to 7 millimeters thick, may completely surround the original bone structure. The new bone can easily be separated from the old cortex by sharp dissection. In the clubbed fingers the only roentgenologic findings are atrophy, spindling and—occasionally—flaring of the terminal phalanges. These findings are in marked contrast to the outstanding proliferative changes of the soft connective tissues of the fingertips. Temple and Jarpin are of the opinion that the flaring of the terminal tufts occurs not only in clubbed fingers but also in normal persons.[a]

The separation between clubbing of fingers and hypertrophic osteoarthritis is [illegible] than was formerly thought. P[illegible]

examination of all patients with clubbed fingers and without pains or swelling of bones reveals many cases with unsuspected ossifying periostitis.

Hypertrophic osteoarthropathy occurring both in humans and in animals, is found in different diseases of the lungs, most frequently in carcinoma of the lungs, either bronchogenic or peripheral, but also in lung abscesses bronchiectasis some mediastinal tumors or even in emphysema. It is remarkably frequent in endothelioma of the pleura, but relatively uncommon in chronic tuberculosis unless secondary bronchiectases have formed. It is only rarely observed in metastatic disease of the lung.[7] In addition, this anomaly is found in cyanotic congenital lesions of the heart and blood vessels, in long-standing subacute bacterial endocarditis, in intestinal diseases such as ulcerative colitis, regional ileitis several forms of steatorrhea, and occasionally in liver cirrhosis. However in the latter diseases, when clubbed fingers are found true osteoarthropathy is usually absent. Even in the exceptional cases of intestinal disease where roentgen examination reveals the presence of periostitis, diffuse pains in the affected bones and arthritic swellings are decidedly rare.

In 144 cases of hypertrophic osteoarthropathy Locke found that 78 per cent represented diseases of the respiratory system, 10 to 15 per cent were due to cardiovascular diseases, 5 to 10 per cent to diseases of the gastrointestinal tract or the liver Wierman[14] and associates analyzed the occurrence of hypertrophic osteoarthropathy in 1,024 patients in whom a pulmonary resection had been performed. Clubbing of fingers and osteoarthropathy occurred in 57 per cent of the pleural mesotheliomas 17.6 per cent of the lung abscesses 10 per cent of the pulmonary cysts 9.5 per cent of the bronchiectases 5.2 per cent of the pulmonary malignancies 0.6 per cent of the cases of tuberculosis.

They never observed this syndrome in benign tumors or in granulomas. In my own experience clubbing of fingers does occur occasionally in Boeck's sarcoids of the lungs.

For the correct evaluation of these statistical figures, it must be stressed that the majority of patients suffered from clubbing of the fingers only In this series, painful edema of long bones due to marked periostitis wit' clear-cut arthralgias and swelling of articulations were, for all practical purposes, limited to the cases of pleural mesothelioma and to true malignant lesions of the lung. This, however, is far from a general rule. Vogl[9] and associates, for instance, report one case of lung abscess with full-blown symptoms and signs of hypertrophic osteoarthropathy which disappeared after successful treatment of the lung abscess with antibiotics.

The acute onset of clubbing of fingers or hypertrophic osteoarthropathy in any patient without apparent cause always warrants a careful search for a cryptic pulmonary malignancy It should be emphasized that in this disease the routine anteroposterior chest x-ray often fails to reveal the lesion. Lateral and oblique views to delineate the hidden areas, e.g., the retrocardiac region, are often necessary

Ray and Fisher[6] have emphasized that even bronchoscopy is often negative in patients with hypertrophic osteoarthropathy due to bronchogenic neoplasm. In 13 out of 14 such patients the tumor originated distal to the segmental bronchi, beyond the eye of the endoscopist.

Finally rare cases of hereditary and familial clubbing and hypertrophic arthropathy must be mentioned.[3] This syndrome is sometimes designated pachydermo-periostosis[1,4] to indicate the presence of thickened skin of scalp, eyelids and hands, together with clubbing of fingers and hyperostosis in the distal parts of the limbs. The newly formed bone fuses with the pre-existing cortex. This familial syndrome, which is hardly a disease, must of course be differentiated from hypertrophic osteoarthropathy Although this familial form occurs predominantly in males, Fairbank mentions a case with characteristic roentgenograms occurring in a woman.

PATHOGENESIS

The pathogenesis of the disease is still unknown. It seems important that unilateral clubbing is found—always at the side of the disease—in aneurysms of the innominate artery in brachial arteriovenous aneurysms and in Pancoast tumors. Thus, local circulatory phenomena must play a dominant role in the etiology of hypertrophic osteoarthropathy. In the clubbed fingers, edema and increased vascularization have been repeatedly observed. The network of dilated arteries and arterioles is especially marked around the ungual process. Mendlowitz has demonstrated that the peripheral blood flow to the bulbous tips of clubbed fingers was increased.[8] In addition, he found that the peripheral blood flow waxed and waned with exacerbations and remissions of the underlying disease.

TREATMENT

After removal of the underlying disease, the clubbing of fingers, the periosteal deposition of new bone and the swelling of the articulations disappear. When new subperiosteal bone has been formed, the latter is gradually incorporated into the bone of the metaphysis and diaphysis. This holds true for the severe forms of hypertrophic osteoarthropathy as occur in carcinoma of the lung and pleural mesothelioma and also for the clubbing of fingers seen in suppurative diseases of the lungs, in chronic empyemas of the pleura, in congenital heart disease with cyanosis, in subacute bacterial endocarditis, in ulcerative colitis and in regional ileitis. On the other hand, if the original condition deteriorates, the arthropathy also becomes more marked. Recurrence of osteoarthropathy sometimes occurs when, following resection of a lung for carcinoma, metastases to the remaining lung or regional lymph nodes ensue. The syndrome does return if there is local recurrence of a pleural mesothelioma.

In patients with inoperable lung or pleural malignancies, in whom the bone and joint pains due to hypertrophic osteoarthropathy constitute a major complaint, corticosteroids may bring temporary symptomatic relief.[9] Recently a remarkable favorable effect of transsection of the intrathoracic part of the vagus nerve on hypertrophic osteoarthropathy has been reported.

Chapter 27

Scleroderma

IN SCLERODERMA THE OUTSTANDING PATHologic change consists of a fibrinoid degeneration of the collagen bundles of the supporting tissue of the body.[2] In the later stages of the disease a subsequent hyaline degeneration of the collagen leads to atrophy of the skin and scar formation. Ultimately as the name scleroderma indicates, hardening of the skin and the subcutaneous tissue results. It should be emphasized that this change of the collagen is not limited to the skin, but is also present in different visceral organs. In many cases of scleroderma marked changes of the collagen bundles of the esophagus lungs, intestine, heart, kidneys and other organs lead to serious disturbances of the functions of these organs.

Although scleroderma may start suddenly in the majority of cases its presence becomes evident only after a long period of prodromal signs. The latter may consist of excessive fatigue with slight fever, a rheumatoid arthritis-like syndrome, peptic ulcer like symptoms and signs, and a Raynaud syndrome (especially frequent).

As a matter of fact the majority of cases of scleroderma, especially in women, are preceded by vasomotor attacks in the fingers which cannot be distinguished from the classical symptoms and signs of Raynaud's syndrome.

In the first stages of the disease the skin is thickened. The swelling of the skin may be so marked that the initial forms of scleroderma are sometimes erroneously diagnosed as renal edema. Soon the skin loses its elasticity and cannot be rolled freely over the underlying structures. In the later stages the atrophic skin is firmly bound to the underlying bone. Usually dark pigmentation of the skin develops, sometimes not only over the affected parts of the skin, but also over the rest of the body. The skin pigmentation in scleroderma may be similar to the pigmentation found in Addison's disease, and in rare cases even pigmentation of the mucous membranes develops.

In scleroderma the changes in the fingers are nearly always in the foreground. After the Raynaud attacks have been in existence for several months or even years, the skin of the fingers does not return to normal any more. Even between the attacks the cyanosis of the fingers and nails persists, the hands remain cold and there is either excessive sweating or absence of sweating in the hands. Then, gradually the typical changes of scleroderma develop.

Severe sclerodermatous changes of the hands are often designated sclerodactyly. In advanced cases of sclerodactyly deep ulcerations localized at the tips of the fingers may develop. The ulcerations show little tendency to heal but when healing is ultimately obtained, depressed scars remain. In many cases felons also develop at the fingertips. Closure of these felons is commonly delayed until one or more calcareous concretions have been extruded. Even in cases of scleroderma without felon-like lesions in the fingertips widespread subcutaneous and periarticular deposition of calcium salts can often be recognized on the roentgenograms. In this so-called syndrome of Thibierge and Weissenbach,[3] calcifications can also, though less frequently, be found in the neighborhood of larger joints and even in the muscular interstitial layers.

On the roentgen photos of patients with scleroderma, apart from the calcium deposits, remarkable mutilations and autoamputations of the terminal phalanges can sometimes be

visualized. In a consecutive series of 31 cases of scleroderma, 18 patients showed sclerodactyly The mutilations in the latter group varied between partial absorption of the tuft of one phalanx to almost complete resorption of all terminal phalanges of both hands. The destruction of the tufts starts distally and progresses proximally [1]

Plate 44b c illustrates that necrosis of the terminal phalanges and partial autoamputations are often present at the same time. It is noteworthy that the necrotic phalanges cause denser shadows on the roentgen photos than the living ones. Living bone contains only 70 per cent of calcium phosphate. Necrotic bone, however calcifies just like any other necrotic tissue and therefore consists nearly 100 per cent of calcium salts. It follows that necrotic bone must cast a more intensive x ray shadow than living bone.

Sometimes para articular calcifications can be visualized, while at the same time remarkable trophic changes of the distal ends of the bones of the forearm are present. A candlestick deformity occasionally observed in scleroderma is highly reminiscent of the bone changes seen in leprosy In the latter ailment this anomaly is considered to be neurotrophic in origin. The candlestick deformity in scleroderma points to the possibility of neurotrophic processes in the pathogenesis of the sclerodermatous lesions.

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Chapter 28

Charcot Joints Neurotrophic Osteoarthropathy

THE IMPORTANCE OF THE NERVOUS SYSTEM for the condition and maintenance of the different body parts is clearly demonstrated by the changes of bones and joints which develop in the course of different neurologic disorders. When the functions of the nervous system are intact, the normal metabolism of the skin, muscles and bones is maintained by a continuous flow of so-called neurotrophic stimuli, arising within the nervous system. In the section on osteoporosis due to immobilization (p 27), the influence of this neurotrophic stimulation has already been mentioned.

Severe neurotrophic changes may occur in tabes dorsalis, especially in the knee joint. They may also occur in the foot, occasionally in the hip and the lower thoracic and lumber spine, but rarely in other articulations. The first sign of the disease is usually an effusion in the joint, which initially may give the impression of an innocent hydrarthros. Gradually the swelling of the affected joint increases and ultimately a bizarre deformation may result. At this point palpation often reveals the presence of an abnormal proliferation of bone within and around the affected articulation. The ligaments of the affected joint are destroyed (PLATE 45a b c) and the patient is usually left with an unstable, flail joint. Broadening of the midportion of the foot is typical. Despite these gross anatomic anomalies there is hardly any pain when the articulation is palpated and moved actively or passively The diagnosis of tabetic arthropathy or Charcot joint is easy when other outstanding signs of tabes dorsalis are present. However, in many cases the very first subjective symptom of this disease consists of a painless swelling of knee or foot. In these circumstances the diagnosis is often missed, although careful examination usually will reveal other characteristic anomalies.[1]

In the first stage of the disease roentgenograms reveal only the presence of separation of the articular surfaces by the fluid accumulation. Later, the neurotrophic arthropathy leads to marked sclerosis and often to grotesque deformation of the bones which form the articulation (PLATE 45a) Calcium deposition within and in the neighborhood of the synovial membrane takes place, finally followed by an irregular undisciplined exuberant proliferation of abnormal bone around the affected joint.

In the lumbar and lower thoracic spine the tabetic arthropathy causes osteosclerosis, especially beneath the articular surfaces. At the same time, there is disorganization of the bone structure with massive new bone formation in the form of dense paravertebral bone masses. The intervertebral spaces ordinarily are narrowed and ankylosis frequently occurs. Comparable neurotrophic arthropathies occur in syringomyelia, leprosy and occasionally in other affections of the nervous system.

Recently, interest in neurotrophic lesions of the skeleton of the foot in diabetes has been revived.[2-4] Many decades ago the neurologic lesions of diabetes due either to neuritis or to vascular changes of the nervous system were designated "pseudotabes diabetica." The trophic ulcers of the sole of the foot of the diabetic and the "mal perforant" of

the tabetic foot certainly exhibit a remarkable similarity In long-standing diabetes roentgen examination often reveals a marked absorption of bone in the tarsus, metatarsus and phalanges of the foot. The cartilage of the joint spaces is eroded and ultimately disappears. These bone changes may be due partly to immobilization, partly to continuous traumatization of the anesthetic diabetic foot and partly to neurotrophic influences. Sclerosis of the arteries of the feet can play only a minor role, because the tarso-metatarsal lesions in the feet of diabetics frequently occur in the presence of normal arterial pulsations in the lower extremities. The neurotrophic factor seems to be important, since sclerosis is frequently seen in association with resorption of the tarsal bones. This combination of osteosclerosis and resorption of bone especially occurs in the calcaneus. However the abnormal new formation of para-articular bone which is characteristic for the tabetic Charcot joint does not occur in the neuropathic changes of the foot in diabetes.

On the other hand, it should be noted that resorption of bone, when limited to the *phalanges* of the diabetic foot, is probably not neurotrophic in origin. The latter destructive lesions are also observed in other diseases and must stem from insufficient vascularization and chronic soft tissue infection. Therefore, resorption of bone in the distal part of the skeleton of the foot in the absence of abnormalities of the tarso-metatarsal skeleton should be differentiated from the diabetic neuropathic osteoarthropathy

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Chapter 29

Skeletal Lesions in Cancer of the Breast, Prostate and Thyroid

A DISCUSSION OF PRIMARY TUMORS OF the bone is outside the scope of this book. It seems appropriate, however to analyze a special group of metastatic malignancies to the bone which are, at least partly amenable to treatment with hormones and other medicaments. To this group belong

1. Metastases of mammary carcinomas, both in women and in men.
2. Carcinoma of the prostate.
3. Carcinoma of the thyroid.

MAMMARY CARCINOMA

LOCALIZATION OF SKELETAL METASTASES

Cancer of the breast has a tendency to metastasize to the skeleton. It is estimated that at autopsy at least 77 per cent of patients with mammary cancer present signs of neoplastic invasion of the skeleton. In some cases extensive spread of metastatic bone lesions may be present even before the primary tumor of the breast can be discovered with certainty by palpation. In other patients the first symptoms and signs of metastatic bone lesions may develop a few weeks or months after the radical mastectomy, whereas sometimes an apparent "cure" may last for one decade or more, before the signs of skeletal metastasis develop. The skeletal metastases of mammary cancer may be localized in any part of the skeleton, but occur most frequently in lumbar spine, pelvis, ribs, femurs and skull.[7,41] Consequently in patients with breast cancer pathologic fractures of these parts of the skeleton are quite common. There is a plausible explanation for this special distribution of the metastatic disease the veins of the mammary glands communicate with the intercostal veins which, in turn, connect with the vertebral veins. The vertebral veins drain the venous blood from the vertebrae pelvis, upper ends of the femurs and skull. No valves are present in this venous system. During coughing and pressing the positive pressure in the thorax easily reverses the blood current in this system of intercommunicating veins. By this mechanism metastases from a mammary cancer may easily reach the spine, ribs, pelvis, femur and skull via the vertebral vessels. Hematogenous metastases may also reach the bones via another route. Deposits in the lung may grow into the pulmonary capillaries, reach the left heart and settle in any part of the skeleton.

The importance of the system of the vertebral veins for the spread of metastases is clearly demonstrated by the observation of patients with mammary cancer in whom widespread bone metastases were found, although at autopsy the lungs were completely free of neoplasm.[7]

For practical purposes it must be pointed out that complaints about pains in the back from a woman who has been operated on for a mammary cancer always point to the possibility of a metastatic lesion of the spine. This certainly holds true when forward and backward bending reveals fixation of the spine.

ROENTGENOLOGIC PICTURE

Skeletal localizations of breast cancer pre-

sent as many other metastatic malignancies for the greater part they appear as osteolytic lesions (PLATE 46c), although true osteoblastic metastases also occur (PLATE 46a, b) Many skeletal metastases—the intertrabecular type of bone invasion—cannot be visualized by roentgenologic methods. In this form of metastasis the bone trabecules are not destroyed but the bone marrow is partially replaced by cancer cells. However intratrabecular bone invasion is relatively uncommon in most cases neoplastic proliferation takes issue from the cancellous bone. Subsequently the cortex is invaded from the marrow cavity Even the osteolytic and osteoblastic metastases only show up on roentgen photos when far reaching changes of the bone structure are present. With the use of modern x ray technique, including laminograms, Bachman and Sproul[3] could find roentgenographic evidence of neoplastic bone involvement in only 15 of 31 patients in whom the autopsy disclosed the presence of vertebral metastases. Collapse of vertebral bodies is one of the frequent manifestations of the disease. In contrast to inflammatory lesions of the vertebral spine, in malignant lesions the intervertebral disk nearly always remains intact, while a paravertebral mass is hardly ever present. However as usual, exceptions to this rule occur cases of malignant involvement of the vertebrae which roentgenologically cannot be differentiated from inflammatory spondylitis being encountered from time to time, especially in older patients. Before actual collapse of a vertebra is visualized on the roentgenograms, invasion and destruction of the pedicles can already be discovered. Invasion of the pedicle by a malignancy becomes manifest in the anterior posterior films in the form of erosion of one of the two oval planes, which can be recognized on the roentgenograms near the upper lateral border of the vertebr ... lateral exposures the pedicle is al ... ed in its entirety and destructive ... be cognized without difficult

The osteolytic lesions ofte ... same time signs of osteoblastic

form of sclerotic patches in the vertebrae or a sclerotic rim surrounding the osteolytic areas. When the skeletal metastases are purely osteolytic and round, they cannot be differentiated from myelomatosis. Especially when such lesions are localized in the skull, metastases of breast cancer are easily confused with multiple myeloma (PLATE 46c) A bone marrow puncture is usually sufficient to solve this problem in differential diagnosis. Needless to say signs of osteoblastic activity strongly militate against the diagnosis of myeloma.

TREATMENT

At the end of the 19th century there were frequent reports of improvement in the condition of patients with metastases of mammary cancer after bilateral oophorectomy At that time it was usually assumed that spontaneous improvement of the condition of a patient with metastatic mammary cancer was caused by extensive metastatic disease of the ovaries In later years, surgical castration was replaced, at least partly, by roentgen castration. Administration of large amounts of androgens also may retard the progress of metastatic mammary cancer However castration is more effective than androgen treatment in suppressing tumor growth in premenopausal women.

Interesting experimental data seemed to provide a satisfactory explanation for the rationale of this treatment. In certain mouse strains mammary cancers develop spontaneously If such mice are treated with female hormones the mammary cancer develops at an earlier age If androgens are administered, the development of the mammary cancer is delayed. Oophorectomy performed when the newborn mice of these strains are only fifteen to twenty days old prevents the development of mam ... cancer however when this operat ... ormed at the age of six to seven ... e preventive action is very much ... These and other experimental ... ed to explain the favorable in ... drogens upon metastatic mam ...

On t ... atedly been

observed that large amounts of estrogens are able to halt the growth of soft tissue metastases of mammary cancer [8,11] In such large doses the estrogenic substances suppress the function of the pituitary The ensuing inhibition of the metastatic spread is evidently more important than the stimulating effect of the estrogens on tumor growth.

Gradually another concept has come to the fore. It is remarkable that androgens have a favorable influence on both postmenopausal osteoporosis and skeletal metastases of mammary cancer These diseases seem to be miles apart, except that both affect mainly spine and pelvis. In later years it has been ascertained that androgens improve the synthesis of protein thereby accelerating the formation of bone matrix. This explains the improvement of postmenopausal osteoporosis by androgen treatment (p 19) It thus seems possible that androgens could delay the growth of skeletal metastases via their influence upon the metabolism of the skeleton.

That androgens modify calcium and phos-
horus metabolism of patients with osteolytic
etastases of mammary cancer cannot be
ubted. In about 15 per cent of women with
h metastases, hypercalcemia exceeding
) mg per cent is found before any treat
it is started. Administration of androgens
large amounts to such hypercalcemic
nts often leads to a decrease of the
rcalcemia. In contrast, in about 10 per
of patients with metastases of breast
r without hypercalcemia, androgen
ent leads to an increase of the serum
n.[8,10] This so-called induced hyper
a is associated with hypercalciuria
percalcemic signs, i.e., apathy ano-
ausea, vomiting and drowsiness often
All this
is influe to indicate that
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cent of the patients without visible osseous metastases.

The doses of androgens which are necessary for the treatment of metastatic disease of breast cancer are larger than the doses advocated for the treatment of postmenopausal osteoporosis. To obtain favorable results, intramuscular injections of testosterone in doses of 50-100 milligrams three times weekly, sometimes even daily must be administered.

The variations of the serum and urinary calcium do not depend on changes of the skeleton alone. Plimpton and Gellhorn recently reported ten cases of cancer of different organs with hypercalcemia, hypophosphatemia and increased alkaline phosphatase of the serum. In seven cases which came to autopsy, no skeletal metastases were found.[12] In the other three cases removal of the primary tumor was followed by a return to normal of serum calcium, phosphorus, and alkaline phosphatase. No parathyroid adenomas were found and no osteitis fibrosa was present in the skeleton. It seems possible that malignant tumors might produce a substance with a vitamin D–like or parathyroid hormone–like action. It is certain, however that the problem of hypercalcemia in malignancy requires much more investigation before reliable conclusions can be made.

In menstruating women it is necessary to perform a roentgen castration or a surgical castration before starting the androgen treatment. Bilateral oophorectomy may be advisable in menopausal women too. Signs of masculinization which necessarily set in when large doses of androgens are given to a non-menstruating woman, can be alleviated by simultaneous administration of estrogens (p 20) Fortunately estrogens are not contraindicated because, as mentioned above in the postmenopausal patients large doses of female hormones can even be used for the treatment of metastatic manifestations of mammary carcinoma.

In the course of the androgen treatment the pains often diminish and even completely

sent as many other metastatic malignancies for the greater part they appear as osteolytic lesions (PLATE 46*c*), although true osteoblastic metastases also occur (PLATE 46*a b*) Many skeletal metastases—the intertrabecular type of bone invasion—cannot be visualized by roentgenologic methods. In this form of metastasis the bone trabecules are not destroyed but the bone marrow is partially replaced by cancer cells. However intratrabecular bone invasion is relatively uncommon in most cases neoplastic proliferation takes issue from the cancellous bone. Subsequently the cortex is invaded from the marrow cavity Even the osteolytic and osteoblastic metastases only show up on roentgen photos when far reaching changes of the bone structure are present. With the use of modern x-ray technique including laminograms, Bachman and Sproul[1] could find roentgenographic evidence of neoplastic bone involvement in only 15 of 31 patients in whom the autopsy disclosed the presence of vertebral metastases Collapse of vertebral bodies is one of the frequent manifestations of the disease. In contrast to inflammatory lesions of the vertebral spine in malignant lesions the intervertebral disk nearly always remains intact, while a paravertebral mass is hardly ever present. However as usual, exceptions to this rule occur cases of malignant involvement of the vertebrae which roentgenologically cannot be differentiated from inflammatory spondylitis being encountered from time to time, especially in older patients. Before actual collapse of a vertebra is visualized on the roentgenograms, invasion and destruction of the pedicles can already be discovered. Invasion of the pedicle by a malignancy becomes manifest in the anterior posterior films in the form of erosion of one of the two oval planes, which can be recognized on the roentgenograms near the upper lateral border of the vertebra. In the lateral exposures the pedicle is always visualized in its entirety and destructive lesions can be recognized without difficulties.

The osteolytic lesions often show at the same time signs of osteoblastic activity in the form of sclerotic patches in the vertebrae or a sclerotic rim surrounding the osteolytic areas. When the skeletal metastases are purely osteolytic and round, they cannot be differentiated from myelomatosis. Especially when such lesions are localized in the skull, metastases of breast cancer are easily confused with multiple myeloma (PLATE 46*c*) A bone marrow puncture is usually sufficient to solve this problem in differential diagnosis. Needless to say signs of osteoblastic activity strongly militate against the diagnosis of myeloma.

TREATMENT

At the end of the 19th century there were frequent reports of improvement in the condition of patients with metastases of mammary cancer after bilateral oophorectomy At that time it was usually assumed that spontaneous improvement of the condition of a patient with metastatic mammary cancer was caused by extensive metastatic disease of the ovaries. In later years, surgical castration was replaced, at least partly by roentgen castration. Administration of large amounts of androgens also may retard the progress of metastatic mammary cancer However, castration is more effective than androgen treatment in suppressing tumor growth in premenopausal women.

Interesting experimental data seemed to provide a satisfactory explanation for the rationale of this treatment. In certain mouse strains mammary cancers develop spontaneously If such mice are treated with female hormones the mammary cancer develops at an earlier age if androgens are administered, the development of the mammary cancer is delayed. Oophorectomy performed when the newborn mice of these strains are only fifteen to twenty days old prevents the development of mammary cancer however when this operation is performed at the age of six to seven months the preventive action is very much decreased. These and other experimental data appeared to explain the favorable influence of androgens upon metastatic mammary disease.

On the other hand, it has repeatedly been

observed that large amounts of estrogens are able to halt the growth of soft tissue metastases of mammary cancer.[4,11] In such large doses the estrogenic substances suppress the function of the pituitary. The ensuing inhibition of the metastatic spread is evidently more important than the stimulating effect of the estrogens on tumor growth.

Gradually another concept has come to the fore. It is remarkable that androgens have a favorable influence on both postmenopausal osteoporosis and skeletal metastases of mammary cancer. These diseases seem to be miles apart, except that both affect mainly spine and pelvis. In later years it has been ascertained that androgens improve the synthesis of protein, thereby accelerating the formation of bone matrix. This explains the improvement of postmenopausal osteoporosis by androgen treatment (p. 19). It thus seems possible that androgens could delay the growth of skeletal metastases via their influence upon the metabolism of the skeleton.

That androgens modify calcium and phosphorus metabolism of patients with osteolytic metastases of mammary cancer cannot be doubted. In about 15 per cent of women with such metastases, hypercalcemia exceeding 11.0 mg per cent is found before any treatment is started. Administration of androgens in large amounts to such hypercalcemic patients often leads to a decrease of the hypercalcemia. In contrast, in about 10 per cent of patients with metastases of breast cancer without hypercalcemia, androgen treatment leads to an increase of the serum calcium.[4,16] This so-called induced hypercalcemia is associated with hypercalciuria and hypercalcemic signs, i.e., apathy, anorexia, nausea, vomiting and drowsiness often develop. All this seems to indicate that androgens influence the metabolism of the skeleton in which these metastases are developing.

In about 50 per cent of the patients with skeletal metastases, the alkaline phosphatase increases during androgen treatment.[9] The same increase was observed in about 20 per cent of the patients without visible osseous metastases.

The doses of androgens which are necessary for the treatment of metastatic disease of breast cancer are larger than the doses advocated for the treatment of postmenopausal osteoporosis. To obtain favorable results, intramuscular injections of testosterone in doses of 50-100 milligrams three times weekly, sometimes even daily, must be administered.

The variations of the serum and urinary calcium do not depend on changes of the skeleton alone. Plimpton and Gellhorn recently reported ten cases of cancer of different organs with hypercalcemia, hypophosphatemia and increased alkaline phosphatase of the serum. In seven cases which came to autopsy no skeletal metastases were found.[18] In the other three cases removal of the primary tumor was followed by a return to normal of serum calcium, phosphorus, and alkaline phosphatase. No parathyroid adenomas were found and no osteitis fibrosa was present in the skeleton. It seems possible that malignant tumors might produce a substance with a vitamin D–like or parathyroid hormone–like action. It is certain, however, that the problem of hypercalcemia in malignancy requires much more investigation before reliable conclusions can be made.

In menstruating women it is necessary to perform a roentgen castration or a surgical castration before starting the androgen treatment. Bilateral oophorectomy may be advisable in menopausal women too. Signs of masculinization, which necessarily set in when large doses of androgens are given to a non-menstruating woman, can be alleviated by simultaneous administration of estrogens (p. 20). Fortunately, estrogens are not contraindicated because, as mentioned above, in the postmenopausal patients large doses of female hormones can even be used for the treatment of metastatic manifestations of mammary carcinoma.

In the course of the androgen treatment the pains often diminish and even compl-

sent as many other metastatic malignancies for the greater part they appear as osteolytic lesions (Plate 46c) although true osteoblastic metastases also occur (Plate 46a b) Many skeletal metastases—the intertrabecular type of bone invasion—cannot be visualized by roentgenologic methods. In this form of metastasis the bone trabecules are not destroyed but the bone marrow is partially replaced by cancer cells. However intratrabecular bone invasion is relatively uncommon in most cases neoplastic proliferation takes issue from the cancellous bone. Subsequently the cortex is invaded from the marrow cavity Even the osteolytic and osteoblastic metastases only show up on roentgen photos when far reaching changes of the bone structure are present. With the use of modern x ray technique, including laminograms, Bachman and Sproul[3] could find roentgenographic evidence of neoplastic bone involvement in only 15 of 31 patients in whom the autopsy disclosed the presence of vertebral metastases. Collapse of vertebral bodies is one of the frequent manifestations of the disease. In contrast to inflammatory lesions of the vertebral spine, in malignant lesions the intervertebral disk nearly always remains intact, while a paravertebral mass is hardly ever present. However as usual, exceptions to this rule occur cases of malignant involvement of the vertebrae which roentgenologically cannot be differentiated from inflammatory spondylitis being encountered from time to time, especially in older patients. Before actual collapse of a vertebra is visualized on the roentgenograms, invasion and destruction of the pedicles can already be discovered. Invasion of the pedicle by a malignancy becomes manifest in the anterior posterior films in the form of erosion of one of the two oval planes, which can be recognized on the roentgenograms near the upper lateral border of the vertebra. In the lateral exposures the pedicle is always visualized in its entirety and destructive lesions can be recognized without difficulties.

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TREATMENT

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On the other hand, it has repeatedly been

loss of libido and frequent hot flushes. Gynecomastia is more marked after estrogen treatment. On the other hand, the effects of orchidectomy or estrogens in carcinoma of the prostate are often better and of much longer duration than the results of oophorectomy or androgens in women with metastases due to cancer of the breast.

In most cases the synthetic estrogen diethylstilbene (Stilbestrol) has been used. Commonly, daily doses of 5 to 30 milligrams of this drug are given. Although well tolerated by many patients, it does produce nausea and vomiting from time to time which may prevent continuation of the treatment. In such cases administration of very large doses, 100 to 300 milligrams daily, can be tried because paradoxically, certain patients who become nauseated from relatively small doses of this drug can tolerate very large doses. Some urologists favor Estinyl or TACE for the treatment of prostatic cancer. Many clinicians prefer estrogen therapy over castration, others have an opposite opinion. There are also urologists who combine both methods of treatment. Needless to say that in patients who do not tolerate e orchidectomy has to be performed.

The improvement after castratio becomes noticeable after a few days, alleviation after estrogen admini appears only after a long interval disappear swollen lymph nodes urination becomes easier and bone improve. In addition, the acid phos of the serum returns to normal, wh alkaline phosphatase increases. The increase must be caused by the oste activity necessary to repair malignan lytic lesions. Objective roentgen evid the improvement of the osteoblastic stases sometimes cannot be elicited patients whose bone pains are con relieved. Remarkable improvement n for many years, although here again rence of the disease cannot be pre not even by prolonged treatment.

The results of bilateral adrenalecton been disappointing.[19] Not enough hypophysectomy in prostatic cancer been performed to permit a definite about the value of this therapeutic ap

THYROID CARCINOMA

Malignant tumors of the thyroid are usually divided into malignant adenoma, papillary carcinoma, adenocarcinoma and anaplastic carcinoma. In this classification the malignant adenoma is the least malignant, the anaplastic carcinoma the most malignant tumor. All thyroid carcinomas irrespective of their malignancy have a tendency to metastasize in the bones.

Roentgenologically, these bone metastases are osteolytic and cystic in character. They practically always start in the cancellous bone, erode the cortex, sometimes destroy part of the bone completely cause localized swelling of the part of the skeleton involved and are occasionally pulsating. However, the formation of pulsating bone metastases is less frequent in thyroid carcinomas than, for instance, in clear cell carcinomas of the kidneys. The metastases allegedly sometimes enlarge during menstruation and preg The bones most liable to be seeded by cancers are skull, spine, pelvis, ribs, st and different long bones,[14,15] especially and humerus. These metastases are oval-shaped, purely osteolytic (PLATE 46d) and well circumscribed. They therefore be caused by any other mal bone metastasis. Since the metasta thyroid cancer never cause periosteal tion, they are rather frequently erron diagnosed as multiple myelomas. Som multiple, fine bone septa are present metastases. This is especially freque metastases to the pelvis, just as is th in plasmocytomas of the iliac bone.

Sometimes the bone metastases of t carcinomas can be favorably influenc radioactive iodine, I^{131} which, like non active iodine, is absorbed by functi

active thyroid cells. Due to its radioactivity I^{131} destroys the cells in which it has been absorbed. It follows that the therapeutic activity of I^{131} is greatest when the cells of the thyroid cancer still function like normal thyroid cells, i.e., in cases where the tumor can still produce colloid with thyroglobulin. In few of the thyroid cancers, except in malignant adenomas, is the I^{131} uptake sufficient to cause significant cytotoxic action.

Malignant adenomas have a follicular structure and freely form colloid, consequently, the histologic structure of these tumors differs very little from the normal thyroid gland. Nevertheless, malignant adenomas are biologically malignant and metastasize freely. Since the histologic structure of the metastases and the original tumor is identical, the daughter tumors histologically appear like normal thyroid tissue. Following a suggestion given by Cohnheim in 1876, in the older literature the malignant adenomas were usually designated "benign metastasing strumas," an expressive but not completely correct term. When these tumors are removed surgically a diagnosis of benign struma is often made until metastases, usually in the bones develop. Malignant adenomas vary greatly in size and appearance but even large tumors are always encapsulated. Their malignant nature is certain when invasion of the blood vessels can be demonstrated. Rather frequently, the patients seek medical advice only after a tumor of the skeleton has developed. In these cases the primary thyroid tumor is so small that it has gone unnoticed by the patient.

The metastases of malignant adenomas are capable of forming thyroglobulin. These malignant deposits must therefore be able to concentrate both iodine and I^{131}. The administration of large doses of I^{131} to such patients results in a destruction of the metastases due to the radiation effects selectively delivered to this area. Such therapeutic effect is especially important because well differentiated malignant adenomas are much less sensitive to x ray treatment than the anaplastic thyroid cancers.

It is sometimes possible to stimulate the hidden propensity to form thyroglobulin, residing in nondifferentiated thyroid cancers, even if their structure is less similar to a normal thyroid gland than the malignant adenomas. It is well known that the uptake of iodine and the formation of thyroglobulin by the thyroid gland is increased by the thyroid stimulating hormone (TSH), elaborated by the anterior pituitary. Production of thyroglobulin, on the other hand, reduces the output of TSH. In other words, the anterior pituitary secretes a hormone which stimulates the thyroid gland, whereas the ensuing secretion of thyroid hormone inhibits the output of TSH. In this way a finely adjusted equilibrium is created and overstimulation of the thyroid gland is prevented.

The thiourea derivatives used for the treatment of hyperthyroidism influence the course of Graves's disease because they modify this reciprocal relationship between thyroid hormone and TSH. Under the influence of thiouracil compounds the formation of thyroglobulin from inorganic iodine is inhibited. In the absence of thyroglobulin formation, the TSH elaboration by the pituitary increases, resulting in an increased inorganic iodine uptake by the thyroid gland. The large quantity of iodine which the thyroid absorbs from the blood, due to the influence of the action of the thiouracil derivatives, is not transformed into thyroglobulin.

On the basis of these physiologic and pharmacologic principles, Rawson has devised the following treatment of potentially functional metastases of thyroid cancer.[14] Patients with inoperable metastases of thyroid cancer are submitted to a total thyroidectomy. In the absence of the thyroid gland no thyroglobulin is produced and the output of TSH by the anterior lobe of the pituitary gland is increased. Thereafter daily doses of 600 milligrams of a thiouracil derivative or of 60 milligrams of mercapto-imidazole are given. Either of these drugs inhibits the formation of thyroglobulin by functionally active metastases of a thyroid cancer and thereby keeps the formation of

TSH at the highest possible level. The excessive production of TSH stimulates the metastases to absorb maximal amounts of iodine. After the thiouracil treatment has been continued for ten weeks—if necessary for several months—a tracer dose of I^{131} is administered. When a sufficient amount of I^{131} is absorbed by the metastases, treatment with radioiodine is indicated, 35 to 200 millicuries of I^{131} being administered.

Since the result of the preparatory treatment with thyroidectomy and thiouracil derivatives depends mainly upon increased endogenous production of TSH by the anterior lobe of the pituitary, the effect of this preparatory treatment can be further improved by the exogenous administration of thyroid stimulating hormone.

This cleverly devised method has succeeded in increasing the iodine uptake of the skeletal metastases of thyroid cancers to such a degree that 39 to 66 metastases of thyroid cancer, which originally did not respond to radioactive treatment, could later be successfully treated with radioactive iodine.[14]

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Chapter 30

Fungus Diseases and Actinomycosis

FUNGUS DISEASES

Fungous diseases may give rise to chronic granulomatous inflammation of the bone. This occurs in blastomycosis,[1,7,9,10] coccidioidomycosis,[4,8,9] torulosis,[6,11] and, less frequently in histoplasmosis.[4] The roentgenologic pictures of bone lesions caused by each of the four are similar and cannot serve for the differential diagnosis between these diseases. Furthermore, the roentgenograms of bone lesions due to fungi often cannot be distinguished from tuberculous lesions.

In the long bones, fungus diseases cause destruction of bone trabecules and replacement of bone substance by granulomatous tissue. Osteolytic lesions with only moderate reactive osteosclerosis result. In children, however marked periosteal bone deposition takes place in the neighborhood of fungus granulomas, which leads to considerable increase of the transverse diameter of the bones. This periosteal bone formation is much more extensive in fungus disease than in tuberculosis of children. In the skeleton of the adults, which is less reactive than the infantile skeleton, fungus disease less easily leads to periosteal bone formation.[7]

In the ribs, fungus infections give rise to osteolytic lesions which frequently manifest themselves as crescent-shaped destructions at the caudal side of the ribs (Plate 48*b* *c*)

In fungus infections of the spine, early involvement of the intervertebral disk with disappearance of the intervertebral space occurs much less frequently than in tuberculosis. On the contrary in fungus diseases the intervertebral disk rather frequently remains intact.[7] The vertebral bodies collapse easily and bone destruction is prominent. Just as in tuberculosis, paravertebral abscesses can be visualized frequently as paravertebral shadows which may even penetrate into the psoas spaces. The paravertebral progression of the abscess, by dissection below the ligaments of the spine, causes involvement of other vertebrae which are not necessarily adjacent to the first involved segment. Thus neighboring vertebrae apparently may be skipped by the fungus infection.

When the fungus diseases are chronic and last for years, the result is ultimately sclerosis of the diseased vertebrae. In these late stages sclerotic collapsed vertebrae may be found. All this notwithstanding, roentgenographic methods usually do not permit a certain and detailed diagnosis of fungus disease of the bone. The diagnosis is easy as soon as fistula formation takes place. Specific fungi can nearly always be cultivated from the pus which can be recovered from these fistulae. Often the organisms can be found in stained sections of the biopsies of the surrounding granulation tissue.

For the diagnosis of coccidioidomycosis excellent serologic immunologic reactions are available. These reactions are less reliable in blastomycosis and histoplasmosis. Skin reactions too may give valuable information in these diseases, but the result of the intradermal reactions is hardly ever decisive. The reactions may remain positive for many decades despite a spontaneous cure of a subclinical infection contracted in childhood. On the other hand, skin reactions may be negative in far advanced cases of fungus diseases. The diagnosis of torula can be made only by biopsy or culture.

Treatment with stilbamidine and 2 hydroxystilbamidine is effective in local or generalized blastomycosis but helps only occasionally in cases of localized histoplasmosis and coccidioidomycosis.[8] The action of iodine gives usually, at best, only temporary relief

ACTINOMYCOSIS

Although half of the cases of actinomycosis are localized in the jaw and neck, the rest of the skeleton is not immune to this disease.[8] Bone involvement takes place by direct extension from lesions in the submucous layers into the skeleton. The jaw is involved by extension from the gingiva, the dorsal vertebrae and ribs from the lungs, the pelvis and lumbar spine from the abdominal viscera. When a chronic infiltration of the lungs is found in the presence of extensive osteolytic lesions of ribs, sternum or spine, the possibility of an actinomycotic lesion—or a fungus infection—must be seriously considered.[8]

In actinomycosis of the spine the vertebral bodies may be diseased, the pedicles and laminae destroyed, but the intervertebral disk usually remains intact.[2,3] Often the transverse processes and the heads of the adjacent ribs are involved. In the acute stages of actinomycosis a vacuolated condition of the vertebrae, so-called "soap-bubble" or "honeycomb appearance," is often present. In the later stages, new bone formation and osteosclerosis are prominent, which usually prevent collapse of the vertebral body.

All this is very different from tuberculosis or salmonellosis of the spine (PLATE 48d), where early destruction of the vertebral body with absorption of the intervertebral disk are the early and outstanding signs.

In actinomycosis, rarefaction of bone rarely exceeds new bone formation. Subperiosteal formation of new bone is especially prominent when the jaw and the ribs are involved. Both in children and in adults the diameter of these skeletal parts increases considerably under the influence of an actinomycotic infection. The ultimate diagnosis of actinomycosis must be based upon biopsy or culture.

Treatment with large doses of penicillin is often effective, but iodine, even by intravenous injection, is usually disappointing.

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Chapter 31

Differential Diagnosis of Bone Lesions

NEEDLESS TO SAY THE DIFFERENTIAL diagnosis of bone diseases requires a careful history and physical examination. In this connection a few points of interest may be mentioned. It is usually possible to exclude the presence of serious lesions of the vertebral column by clinical examination. When the spine can be moved freely forward, backward, to the left and to the right without undue fixation, roentgen examination will only rarely reveal an abnormality Pain in the spine evoked by pressure on the head or shoulders is noticed only long after fixation of the vertebral column has occurred. The same holds true for pain resulting from coughing or from coming down on the heels with a shock. Gibbus formation also develops only in the later stages of a spinal disease. Pain in one of the extremities that results from coughing may be a relatively early sign of bone disease thus, however is specific only when a phlebitis can be excluded.

Palpation can be used for the diagnosis of arthritis. Inflammation of the synovial membrane of the shoulder joint is present when pain results from pressing on the fissure between deltoid muscle and trapezius muscle of the elbow joint from pressure both medially and laterally to the olecranon of the wrist joint from pressure just distal to the terminal part of the radius and ulna of the hip joint from pressure below the Poupart ligament in the groin, of the knee joint from pressure on the lateral ends of the articular space just below the condyles of the femur and of the calcaneus joint from pressure at both sides of the Achilles tendon.

The consistency of tumors may be of diagnostic importance. Myelomas which break out of the bones are always soft in consistency lymphomas are firm. Hypernephroma metastases may be pulsating

Usually the physical examination is greatly restricted by the severe pains on movement present in the majority of bone diseases. All in all, a physical examination is hardly ever sufficient for the recognition of the character of a skeletal disease. There are very few exceptions to the rule that for the correct diagnosis of the diseases of the skeleton, a careful roentgen examination and exact determinations of calcium, phosphorus and both alkaline and acid phosphatase of the serum must be performed. In most cases, examination of the calcium and phosphorus excretion in the urine on a calcium poor (Bauer Aub) diet is also indicated.

ROENTGENOLOGIC DIFFERENTIATION OF BONE LESIONS

ON GENERALIZED RESORPTION OF BONE

At roentgenologic examination markedly increased bone resorption, irrespective of the cause of the deossification, can manifest itself only as decalcification. There are many different diseases which may lead to extensive resorption of bone.

If deossification is caused by insufficient formation of bone matrix, *osteoporosis* results. This is especially frequent in women in the postmenopausal age. In males a comparable condition hardly ever occurs. However both males and females may be affected by osteoporosis due to senility immobilization, Cushing's syndrome, treatment with corticosteroids, avitaminosis C etc. In all of these conditions the formation of bone matrix is decreased.

In *postmenopausal osteoporosis* (p 15)

the generalized loss of bone substance is limited to the spine, pelvis and ribs. The skeleton of the skull and the extremities remains intact (PLATE 1d)

In postmenopausal osteoporosis just as in other conditions where the resistance of the vertebral column in its entirety is weakened, special changes of the vertebral bodies and the intervertebral disks result. In the initial stages of the disease, multiple herniations of the nucleus pulposus into the softened vertebral body may develop. This results in the formation of so-called Schmorl's nodules (PLATE 1c)

When the resorption of vertebral bone substance has become more intense, the horizontal trabecules of the vertebrae disappear before the vertical trabecular columns are attacked. Hence, the appearance of a vertical striation of the skeleton of the vertebrae is an early sign of bone resorption in the vertebral bodies (PLATE 5c)

In the later stages of osteoporosis the structure of the vertebral bodies in the lumbar part of the spine may become so weak that the elastic intervertebral disks impinge upon both the superior and the inferior aspect of the vertebra. Then the vertical diameter of the intervertebral disk increases while the vertebral body becomes thinner and thinner. This impingement is most marked in the central part of the lumbar vertebrae, resulting in so-called hourglass or fish vertebrae (PLATE 1a) allegedly because the line of gravity of the body runs through the central part of the lumbar spine. More important for the formation of fish vertebrae is the pressure of the centrally situated nucleus pulposus, which has more expansile strength than the rest of the disk.

In the thoracic spine, wedging of the vertebral bodies develops, i.e., the anterior part of the vertebrae is more compressed than the posterior part, apparently because the line of gravity of the body traverses the anterior part of the thoracic vertebral bodies. The vertical diameter of the intervertebral disks of the thoracic vertebrae does not increase (PLATE 2a)

The contrast between the marked bone resorption in the spine, pelvis and ribs and the normal bone structure of skull and extremities is highly important for differential diagnostic purposes. By this localization, postmenopausal osteoporosis can be distinguished from multiple myeloma and other diseases with extensive deossification. The roentgenologic picture of the compressed vertebral bodies in postmenopausal osteoporosis may be very similar to that in multiple myeloma (PLATE 2b) in osteomalacia, in Gaucher's disease (PLATE 1b), or even in hypervitaminosis D (PLATE 5c) It follows that for the diagnosis of postmenopausal osteoporosis, roentgenologic examination of spine, pelvis and ribs is not sufficient. A complete skeletal survey is always necessary since osteolytic lesions in the extremities or in the skull exclude, for all practical purposes, the diagnosis of this disease. Even if the osteoporotic lesions are limited to the axial skeleton, examination of calcium and phosphorus metabolism, bone marrow puncture, and search for Bence Jones protein and hyperglobulinemia are still necessary before treatment of postmenopausal osteoporosis is started.

Postmenopausal osteoporosis in males is very rare indeed. In such instances multiple myeloma or one of the other diseases mentioned above is usually present.

In senile individuals the synthesis of bone matrix is also impaired. It is clinically important that *senile osteoporosis* (p. 21) just like postmenopausal osteoporosis, occurs much more frequently in women than in men. It is probable that in all older women with senile osteoporosis, a combination of senile and postmenopausal osteoporosis actually exists. This explains why the osteoporosis in senile osteoporosis also mainly involves the spine, pelvis and ribs, even if a moderate amount may be seen in the skull and extremities. The minor deossification in the peripheral skeleton is then the result of senile osteoporosis, while the osteoporosis in the spine, skull and ribs is a combination of senile and postmenopausal osteoporosis.

In *Cushing's syndrome* (p 22) just as in

the postmenopausal condition, the osteoporosis is mainly localized in the spine, pelvis and ribs. However, in Cushing's syndrome bone resorption in the calvarium is frequently present. The diagnosis of osteoporosis due to Cushing's syndrome is usually easy because, apart from the skeletal anomaly other manifestations of hyperfunction of the adrenal cortex are also present. Similar osteoporosis develops in patients who have been treated with corticosteroids for a period of several months. In this iatrogenic hypercorticism marked resorption of bone in the skull also takes place.

In *avitaminosis C* a deficient synthesis of collagen is present, the deposition of bone matrix suffers, and osteoporosis results. Other anomalies of the skeleton, especially periosteal hematomas (which eventually calcify) are also found (PLATE 2c)

In *osteomalacia* (p 30) there is widespread decrease of bone salts within the skeleton. In this condition normal bone matrix is produced, but in the absence of calcium or phosphate no ossification of the bone matrix can take place. In histologic preparations the uncalcified bone matrix presents as broad osteoid zones surrounding the bone trabecules. Roentgenologically the condition of the skeleton in osteomalacia may be reminiscent of postmenopausal osteoporosis, except for the widespread involvement of extremities and often also of the skull. The thinning and lamination of the cortex of the extremities, (PLATES 2e 3b) the presence of symmetric Milkman's fissures in the cortex of the long bones (PLATE 2d) and the changes of the shape of the lesser pelvis (PLATES 4a 5a) will often permit the differentiation between osteomalacia and osteoporosis.

Examination of the calcium, phosphorus and alkaline phosphatase content of the serum is important for the differential diagnosis. In postmenopausal osteoporosis, calcium, phosphorus and alkaline phosphatase of the serum are normal. By way of contrast, in osteomalacia the calcium and phosphorus content of serum usually are low and the alkaline phosphatase of the serum is nearly always increased.

The generalized resorption of bone due to excessive osteoclastic action seen in *Recklinghausen's bone disease* (p 59) changes the structure of the whole skeleton. Apart from the thinning of the bone cortex and the destruction of the cancellous bone, giant cell tumors (PLATES 7a 8a b 10a) and cysts can often be found. In addition, subperiosteal resorption of bone is an outstanding feature of the advanced stages of the disease. This is most clearly visible in the phalanges (PLATE 10a) but extensive subperiosteal resorption of bone is also found in the lateral part of the clavicles (PLATE 10b), in the metaphysis of the tibiae (PLATE 10c) and humeri, along the sacroiliac joints, and sometimes in other locations. The disappearance of the lamina dura of the teeth is also due to subperiosteal bone resorption (PLATE 11c, d)

Since Recklinghausen's bone disease is caused by hyperparathyroidism, the classical biochemical syndrome of increase of serum and urinary calcium, decrease of serum phosphorus and increase of urinary phosphorus, together with an increase of the alkaline phosphatase, will be present. In this disease, either one or more parathyroid adenomas or a generalized clear cell hyperplasia of all parathyroids will be found at operation. Rarely, a parathyroid carcinoma is the cause of the disease.

The bone lesion found in chronic long standing uremia with acidosis may sometimes be confused with Recklinghausen's bone disease. This renal osteitis fibrosa occurs mainly in children, being relatively rare in adults. Generalized bone resorption and calcium metastases, especially in the periarticular tissues (PLATE 12c 13a) are the outstanding features. Subperiosteal bone resorption is present, exactly as in hyperparathyroidism. In children there is always a delay of the closure of the epiphyseal disks. The lack of ossification of the epiphyseal disks is reminiscent of rickets—the designation renal rickets" has often been used. Th however, is erroneous. Th

of the epiphyseal disks is always symmetric in rickets, but often asymmetric in chronic uremia. In the latter disease the architecture of the metaphysis is much more abnormal than in rickets. A so-called woolly metaphyseal part of the epiphyseal disks results, which does not occur in rickets.

In contrast to genuine rickets, in renal osteitis fibrosa there is often destruction of the metaphysis, so that the diaphysis of the bone penetrates the metaphysis and the swollen epiphyseal disk and impinges upon the epiphysis (Plate 12*a*, *b*). This never occurs in rickets. Histologically the bone lesion in uremia consists mainly of osteitis fibrosa, whereas broadened osteoid zones are present only in small numbers and remain in the background.

Special differential diagnostic difficulties arise when clear-cut uremia develops in a patient with hyperparathyroidism. In doubtful cases the presence of osteoclastomas is decisive. These giant cell tumors occur only in hyperparathyroidism and not in renal osteitis fibrosa. Simple bone cysts, however are found in both conditions.

In children, delay in the closure of the epiphyseal disks favors the diagnosis of renal osteofibrosis, because in the relatively rare cases of hyperparathyroidism in children, the maturation of the skeleton remains completely normal. In chronic uremia with osteofibrosis, the biochemical signs of uremia will never fail to be present. The serum calcium and the urinary calcium will be low the serum phosphorus very high all in marked contrast to the biochemical changes in hyperparathyroidism. Unfortunately this difference may disappear when the patient with hyperparathyroidism develops uremia.

Generalized *chief* cell hyperplasia of the parathyroids may be found at the autopsy of uremic patients. In this condition one or more parathyroid adenomas or a generalized *clear* cell hyperplasia of all parathyroids are never present.

Although in the later stages of *Paget's disease* thickening of the bone cortex and other roentgenologic signs of osteosclerosis prevail (Plates 16, 17*c* 18*c* *d*, 21) both destruction and hasty reconstruction of bone usually run side by side (Plates 15*a* 17*a*). It can be expected that from time to time in a patient with osteitis deformans the osteolytic phase may prevail over the new formation of *abnormal* bone. This occasionally is encountered in Paget's disease of the skull. Under these circumstances large areas of bone resorption can be visualized in the calvarium (Plate 17*a*). This condition is known as *osteoporosis circumscripta cranii* (p. 121). In the later stages of this disease the resorption of bone may involve the skull in its entirety (Plate 28*a*).

For the differential diagnosis of this disease, *lipoidgranuloma* (Plate 22*a*) or *eosinophilic histiocytosis of the skull* (p. 127) must be considered. In certain instances these granulomas, which commonly lead to cystlike lesions, may involve nearly the whole calvarium and may appear similar to osteoporosis circumscripta cranii.

In *multiple myeloma* (p. 157) proliferation of large and immature plasma cell-like elements, so-called myeloma cells, exists everywhere in the bone marrow. In addition to this generalized myelomatosis, tumor-like accumulations of myeloma cells, so-called plasmocytomas, are often present. Generalized myelomatosis causes destruction of the secondary bone trabecules and thinning of the cortex which, on the x ray, present as generalized resorption of bone or "decalcification" (Plates 35*a*, 36*a*). Contrariwise, the plasmocytomas present on the roentgenograms as punched-out, round osteolytic lesions (Plate 36*c*). In most cases of multiple myeloma, both round defects and generalized resorption of bone can be visualized on the x rays (Plates 35*a* 37*a*, *b*). The plasmocytoma formation, however, may remain in the background, and in such cases the x ray findings in multiple myeloma are limited to generalized bone resorption. Since 40 per cent of the calcium of the skeleton must be resorbed before the loss of bone

substance can be discovered by x ray examination, the skeleton of a patient with generalized myelomatosis, but without plasmocytomas, may occasionally appear normal.

The bone lesions of multiple myeloma are purely osteolytic. As soon as partial osteosclerosis is found, even when only an osteosclerotic ring is present around the osteolytic lesion, myeloma should not be diagnosed.

In *long standing immobilization* (p 26) *hypervitaminosis D* (PLATE 5c) *widespread rheumatoid arthritis* some cases of *Boeck's sarcoidosis* (p 99), and rare cases of *hypoparathyroidism* (PLATES 14b 15b c), generalized bone resorption may be present and may give rise to considerable differential diagnostic difficulties. In many cases, study of the calcium and phosphorus metabolism will reveal important clues which may lead to a correct diagnosis (p 217)

The skeletal destruction caused by reticulum cell sarcoma, other lymphomas or malignancies is rarely so extensive that it could be confused with conditions in which true generalized resorption of bone takes place. In *leukemia* too (p 151) generalized resorption of bone substance occurs much less frequently than might be expected. This has mainly been observed in isolated cases of infantile leukemia. In the infantile forms of acute or subacute leukemia, usually lymphatic in nature, symmetric extensive destruction of bone trabecules in the metaphyseal part of the long bones is a much more frequent sign (PLATES 30d e f) This characteristic roentgen picture can be confused only with metastasizing *neuroblastomas* In addition, there exists a certain similarity with the bone resorption in the metaphysis of patients with avitaminosis C. However the differential diagnostic difficulties between leukemia and *scurvy* (p. 25) can usually be solved very easily

Generalized resorption of bone is constantly found in patients with anterior pituitary insufficiency so-called *Sheehan's disease* It also occurs in *acromegaly* and in *Graves's disease* The intensity of the roentgenologic bone resorption in hyperthyroidism is less intense than in hypopituitarism. Generalized absorption of bone is a constant phenomenon in *osteogenesis imperfecta* so-called fragility of bones.

Several groups of diseases exist in which the diameter of a larger part of a bone in its entirety may be increased. At the same time the cortex is thinned and marked absorption of the trabecules has taken place the normal structure of the cancellous bone has been replaced by a homogenous shadow This condition, always due to the proliferation of an abnormal tissue within the bone marrow cavity is found in *polyostotic fibrous dysplasia* (PLATES 24, 25a) some forms of *congenital hemolytic anemia* (PLATES 29b c) and *Gaucher's disease* (PLATE 39) Comparable roentgenologic findings may be present in *actinomycosis* and in *infantile leukemia*. Marked elevation of the periosteum occurs in the latter disease and will usually point to the correct diagnosis.

The skeletal changes which can be elicited in certain cases of congenital hemolytic anemias (p 142) are caused by the proliferation of the erythroblastic bone marrow The increased mass of this substance not only causes thinning of the cortex of the bones but, at the same time, increases the diameter of the marrow cavity On the roentgenograms the transverse diameter of the small bones of the hands and feet is markedly enlarged (PLATE 29b c) In addition, osteolytic areas due to increased destruction of the bone trabecules of the cancellous bone under the influence of the proliferating bone marrow can be visualized (PLATE 30a b c) The irritation of the periosteum of the skull by the proliferating erythroblastic tissue in the diploë causes the eruption of vertical bone spicules, taking issue from the external table. The result is a so-called hair-brush skull (PLATE 29a)

Sometimes proliferation of the erythroblastic bone marrow compromises the solidity of the vertebrae and causes the destruction

of large numbers of bone trabecules. As is seen in all cases of bone resorption in the spine, *the horizontal bone trabecules of the* vertebral bodies disappear first. In the initial phase of generalized bone resorption in the spine, a vertical striation of the vertebrae results (PLATE 5*c*), while in later stages hour glass formation of the lumbar vertebrae (PLATE 1*a*) and wedging of the thoracic vertebrae (PLATE 2*a*) are found.

The bone lesions in hemolytic anemia are most marked in *thalassemia* (p 142) and least marked in *spherocytic jaundice* (p 145) *Sickle cell anemia* (p 144) has an intermediary position. When the hemolytic anemia has lasted for many years, the resorption of bone may make place for osteosclerotic changes. Since most patients with thalassemia die young, secondary osteosclerosis is hardly ever encountered in this disease. Patients with sickle cell anemia may occasionally reach middle age and, *in such cases, osteosclerosis* may ultimately ensue (PLATE 29*d*) Bone infarction in the upper part of the femur is found in patients with combined sickle cell trait–thalassemia disease. Changes of the configuration of the femoral head, reminiscent of osteoarthritis (PLATE 29*e*) are not rare at all.

In *Gaucher's disease* proliferation of the reticulum cells, loaded with kerasin, a specific lipoid, involves not only the spleen, liver and lymph nodes, but also the bone marrow and occasionally the posterior lobe of the pituitary The *marked proliferation of* Gaucher cells in the bone marrow facilitates the diagnosis, because puncture of the sternal marrow usually reveals the presence of larger Gaucher cells amidst the normal bone marrow cells.

Although Gaucher cells proliferate through the entirety of the bone marrow there are certain locations, nevertheless, where this abnormal process is especially intense. This holds true for the distal ends of the femur where, under the influence of the proliferating Gaucher cells, patchy destruction of the cancellous bone and thinning of the cortex are found (PLATE 39) In addition, the transverse diameter of the distal metaphyseal part of the femur frequently increases in size. This swollen distal part of the femur is commonly compared to an Erlenmeyer flask. The frequent localization of Gaucher's disease in the head *of the femur* causes bone changes reminiscent of bone infarction. In the later stages, the changes of the femoral head may simulate osteoarthritis or Legg Perthes' disease (PLATE 40*a*) Less common are comparable changes of the head of the humerus. Collapse of the vertebrae is relatively rare in Gaucher's disease but does occur (PLATE 1*b*) Generalized bone resorption in the bones of the extremities and the hands may also be present (PLATE 40*b* *c*)

ON OSTEOSCLEROTIC LESIONS

The most frequent cause of osteosclerotic bone lesions is probably *Paget's disease* The basic pathology of the Paget lesion consists of thickening of the cortex and complete disorganization of the architecture of the cancellous bone (PLATES 18*a* *b* 19*b*) In the later stages of the disease the sclerosis of the cortex and the compression of the cancellous part of the bone may both be progressive. Ultimately, the *normal roentgenologic structure of the* skeleton disappears completely and a sclerotic tube or plate of bone remains. The abnormally thick and sclerotic cortex of the *humerus of a patient with Paget's disease* is shown on PLATE 17*c* In the clavicle, the osteitis deformans has already reached the final sclerotic stage. Due to the progressive spread of the cortical osteosclerosis, the spongiosa has been completely replaced by sclerotic bone. Ultimately, the same process will also replace the cancellous bone of the humerus.

Both in the pelvis and in the spine, osteitis deformans frequently gives rise to osteosclerotic lesions. PLATE 16 shows osteosclerotic Paget's disease of the left half of the pelvis. *Osteosclerosis of vertebral bodies leads* to the formation of so-called ivory vertebrae (PLATES 17*b* 18*d*)

In most instances it is impossible to decide whether osteosclerosis in general or ivory

vertebrae in particular indicate the presence of osteosclerotic Paget's disease. Other diseases, especially metastatic malignancies (PLATE 47), lymphomatous lesions (PLATE 31b), polyostotic dysplasia, and megakaryocytic leukemia (PLATE 34a b), can give rise to osteosclerotic manifestations that cannot be differentiated from the sclerotic forms of osteitis deformans

The majority of the cases of Paget's disease are polyostotic in nature. Thus, when the ivory vertebrae are due to Paget's disease, it will often be possible to demonstrate typical nonsclerotic manifestations of this ailment in other parts of the skeleton. If the latter is the case, then it is highly probable that the ivory vertebrae are a manifestation of osteitis deformans. On the other hand, osteosclerosis of the ribs and skeleton of the hand speaks against the presence of Paget's disease, since osteitis deformans hardly ever gives rise to roentgenologic changes of these parts of the skeleton (see, however PLATE 19c d e)

Carcinoma of the prostate (PLATE 47) *the bronchus the stomach and the mammary gland* (PLATE 46a b) are the most common causes of osteoblastic malignant metastases. Occasionally the metastases of other tumors, even of malignant melanoma, have proved to be sclerotic in nature. The diagnosis of carcinoma of the prostate may be revealed by rectal examination, especially if there is malignant infiltration of the seminal vesicles. Unfortunately, carcinoma of the prostate has a tendency to start in the peripheral parts of the gland, which cannot be reached too easily by the palpating finger In addition, this tumor usually grows in a ventral direction toward the urinary bladder Thus palpation often fails to reveal the malignant nature of a prostatic enlargement. The high alkaline phosphatase of the serum in Paget's disease and the high acid phosphatase in metastases of cancer of the prostate are signs of great diagnostic value.

Roentgenologically the differential diagnosis between osteoblastic metastases and osteosclerotic Paget's disease can often be made. In the initial stages of osteitis deformans the cortex of the bone is markedly thickened, while the cancellous bone has an irregular, coarse architecture (PLATES 16, 18a) In contrast, osteoblastic metastases of malignant disease start as sclerotic patches which, in the initial stage, cannot be differentiated from normal bone islands. Gradually, the patchy sclerotic metastatic areas become confluent and ultimately the affected bone, in its entirety, becomes sclerotic. Furthermore, in the initial stages of Paget's disease the diameter of the bone increases (PLATES 16 20), whereas in osteoblastic metastases the diameter of the bone does not change as long as the disease presents only as *multiple osteoblastic islands. In the later* stages of malignant disease when the entire bone has become sclerotic, the diameter also gradually increases.

All this can be well followed in the pubic and ischial bones where both Paget's disease and osteoblastic metastases frequently occur Thickening of the cortex with increase of the diameter of the bone favors the first disease patchy osteosclerotic areas without increase of the normal diameter of the bone indicate the presence of a metastatic malignancy

Notwithstanding all these differential diagnostic data, almost insoluble problems may present themselves. The case of a patient with typical multiple myeloma may be cited in which x ray examination of the spine revealed the presence of two ivory vertebrae. At autopsy the latter were proven to have been caused by Paget's disease, although in the rest of the skeleton no other manifestations of osteitis deformans were found. Everywhere the bone marrow was replaced by wildly proliferating myeloma tissue.

In the presence of possible osteoblastic metastases of a carcinoma of the bronchus, stomach, etc., the search for the primary tumor will require the current diagnostic roentgenologic procedures, together with bronchoscopy gastric analysis, scalenus biopsy etc.

Osteosclerotic bone lesions due to *Hodgkin's disease* (PLATES 31b 32)—occasionally due to one of the other lymphomatous diseases

—cannot be differentiated roentgenologically from osteoblastic carcinomatosis or sclerotic Paget's disease. The diagnosis will be easy when palpable lymph nodes are present and a biopsy can be performed. Occasionally osteosclerosis is the first initial manifestation of Hodgkin's disease. In such cases fever of unknown origin, especially a Pel-Ebstein type of periodic fever attack, is an important point in favor of Hodgkin's disease. It must be added, however, that malignancies, too—especially *clear-cell* carcinomas of the kidneys, bronchogenic carcinoma and many other tumors—may lead to feverish reactions. Splenomegaly is common in Hodgkin's disease, but rare in carcinoma. Marked eosinophilia, frequent in Hodgkin's disease, also occurs in cancer metastases, particularly in bronchogenic carcinoma. Widespread osteosclerosis involving the *greater* part of the skeleton and combined with marked eosinophilia usually indicates Hodgkin's disease. In carcinoma, the osteosclerosis is commonly limited to relatively few bones.

Notwithstanding these and other diagnostic points, the differentiation between osteosclerosis due to Hodgkin's disease and a malignancy may be impossible. This holds true, for instance, in cases of compression of the cord due to Hodgkin's disease in the presence of one or two ivory vertebrae, but without any other detectable sign of a lymphoma. In such cases only the histologic character of the tissue removed at laminectomy may lead to the final diagnosis.

The diagnostic difficulties are increased by the osteosclerosis which follows intense *roentgen treatment*. A patient with Hodgkin's disease may have received such treatment to alleviate severe pains in the back. When the roentgen examination, repeated a few months later, reveals that sclerosis of the vertebrae is developing in the field of radiation, it is often impossible to decide whether this anomaly stems from involvement of the vertebrae by Hodgkin's *disease or whether* it is an after-effect of the roentgen treatment. If, however, the vertebral bodies show combined sclerotic and osteolytic lesions, the changes are probably due to Hodgkin's disease and not to the previous radiation therapy.

In long-standing *chronic leukemia*, myelofibrosis rather frequently develops. Osteosclerosis, however, is rare because secondary calcification or ossification of the leukemic myelofibrosis hardly ever takes place. Generalized osteosclerosis combined with marked eosinophilia is usually caused by Hodgkin's disease and not by an eosinophilic leukemia.

The combination of a widespread osteosclerosis and a leukemoid blood picture without marked eosinophilia is often found in the disease that bears the various designations *aleukemic megakaryocytic myelosis, agnogenic myeloid metaplasia* or *osteosclerotic anemia*. In this remarkable syndrome, osteosclerosis is an early sign. At the same time, hepatosplenomegaly and anemia are present, usually combined with leukopenia, poikilocytosis, and normoblastosis. In the majority of cases the size of the spleen ultimately becomes enormous and is comparable to the tremendous spleens found in many cases of chronic myeloid leukemia, Gaucher's disease and kala-azar. A leukoerythroblastic leukemoid blood picture is found in the later stages of the disease. A hemolytic anemia is a very frequent complication, manifesting itself by reticulocytosis, increased urobilinuria and indirect hyperbilirubinemia. A positive *Coombs test is only rarely present.*

Aleukemic megakaryocytic myelosis may last for many years. Autopsy reveals the presence of a true megakaryocytic leukemia, not of a myelocytic or myeloblastic leukemia. This is why in the peripheral blood only a leukemoid and never a leukemic blood picture is found (p. 154). The finding of megakaryocytes on splenic puncture is pathognomonic of the disease. When hemolytic anemia develops in the course of the disease, corticosteroids should be given. Ultimately a *splenectomy may be necessary.*

The osteosclerosis which develops in the course of aleukemic megakaryocytic myelosis

is often extensive. The bones involved, especially femurs, pelvis, and spine, may become homogeneously sclerotic. Rather frequently a mottled appearance is found owing to the presence of osteofibrotic areas within the osteosclerotic bone. In other cases only part of the skeleton is sclerotic, especially the spine (Plate 34a, b) In other bones myelofibrosis, manifesting as resorption of bone, may be the outstanding characteristic (Plate 34c d)

The clinical picture of *osteopetrosis* marble bone disease, or *Albers-Schönberg's* disease is different in children and adults. In infants and children, this disease is usually fatal within a few years. Severe anemia, leukemoid reactions, compression of cranial nerves and intercurrent infections are the common causes of death.

In both the infantile and the adult forms, the cancellous bone disappears partially or completely and the greater part of the skeleton is transformed into structureless chalky tubes and plates. Often in the sclerotic bone of the extremities a coarse vertical striation is present, usually referred to as "celery bones." In the pelvis, circular rather than vertical striations are found (Plate 43) The diameter of the distal ends of the long bones is markedly increased in size. This leads to clubbing (Plate 41a, c) which is also constantly present in the posterior clinoid processes of the sella turcica (Plate 41b)

The marble bones in Albers-Schönberg's disease, though transformed to thick radiopaque tubes (Plate 41a c) are less solid than normal, and pathologic fractures commonly occur The resilience of the bones depends upon the form and structure of the special arrangement of the secondary bone trabecules. The vertical arrangement of the abnormally thickened primitive bone trabecules, apparent in the "celery bones," does not offer sufficient resistance against traumatic influences even in the harmless osteopetrosis of adults, pathologic fractures occur after apparently insignificant accidents.

Osteopetrosis is nearly always symptomless in adults. Here, as a rule, the osteopetrosis is found incidentally when, for some ailment usually not connected with the skeleton, a roentgenologic examination is performed. In adults, both the clubbing of the distal parts of the bones of the extremities and the encroachment on the cranial foramina are much less marked than in children. Whereas in children the entire vertebral bodies become sclerotic, in the adult form, both the superior and inferior terminal plates are tremendously thickened, but an intermediate layer of cancellous bone always remains. The ensuing formation of "sandwich vertebrae" is typical for osteopetrosis of the adults (Plate 43) In other bones too the marrow cavity may not be completely obliterated (Plate 42b c)

The changes in the skeleton which follow the inhalation or ingestion of *fluoride* in humans and animals are similar to osteopetrosis. This disease occurs mainly among workers in factories where cryolith is processed. The ensuing sclerosis of the skeleton is very similar to the bone changes found in Albers-Schönberg's disease, except that in fluorosis the surface of the bones is irregular and spicular In the latter disease "sandwich vertebrae" may also develop and a tendency to pathologic fractures may exist.

Polyostotic fibrous dysplasia and even *lipoidgranulomatosis* may ultimately terminate as osteosclerotic lesions (Plate 25b) This becomes apparent in *leontiasis ossea* which sometimes is caused by the cranial localization of fibrous dysplasia (Plate 28b) In these cases marked osteosclerosis of the skullbasis and facial bones exists (Plate 27c)

Osteosclerosis, usually patchy in character, may be the terminal phase of chronic inflammatory disease of the bone. This is the case in *tuberculosis salmonellosis syphilis* (Plate 48a) and other diseases. Inflammatory bone lesions are frequently localized in the spine. Destruction of the vertebral disks is an early manifestation of inflammatory spinal disease (Plate 48d)

Osteosclerosis of the iliac bone of unknown

origin (osteitis condensans ilei) is, fortunately, a rare disease.

In the few patients with sickle cell anemia who live beyond the age of 40 years, the skeleton may ultimately become sclerotic. In young patients the proliferation of the bone marrow present in all hemolytic anemias leads to weakening of cortex and cancellous bone. In the lumbar spine, hourglass vertebrae may be present in the dorsal spine wedging of vertebral bodies results. Finally, in older patients with sickle cell anemia, these hourglass vertebrae may become sclerotic (PLATE 29*d*)

CYSTS AND CYSTLIKE LESIONS

Simple bone cysts are usually roundish or oval osteolytic lesions with smooth contours. Although congenital bone cysts, so-called unicameral cysts, located in the metaphysis, are rather frequently encountered, most of the bone cysts are traumatic in nature and occur in nearly all diseases where generalized bone resorption is present. A slight trauma, which would not cause any changes in normal bone may lead, via a hemorrhage, to cyst formation in debilitated bones.

In *Recklinghausen's bone disease* cysts frequently occur Recklinghausen even gave the name osteitis fibrosa cystica generalisata to the disease he described. Not all the cystic lesions observed in Recklinghausen's bone disease are actually cysts. Part of these so-called cysts in hyperparathyroidism are giant cell tumors or osteoclastomas (PLATES 8*c* 11*a*) Many giant cell tumors exhibit the well known typical septate appearance (PLATE 8*b*) but others present on the x rays as simple cysts (PLATES 8*c* 11*a*) Osteoclastomas rapidly ossify after the parathyroid adenomas have been removed, whereas true cysts persist in an unchanged condition after the operation.

In the presence of a cystic lesion of the skeleton, the possibility of an osteoclastoma due to hyperparathyroidism must always be considered. In each case a careful investigation of the calcium and phosphorus metabolism is in order The biochemical characteristics of hyperparathyroidism have been repeatedly mentioned (p 65) This investigation is also necessary when only one cyst is found in the presence of a completely normal x ray appearance of the rest of the skeleton. Long before the resorption of bone has gone so far that the loss of bone substance can be visualized by x ray examination, the solidity of the skeleton has already suffered and a tendency to the formation of traumatic bone cysts exists. A good example of this is the patient with hyperparathyroidism and pseudo-diabetes insipidus mentioned before (p 79) where the only bone lesion ever discovered was limited to one osteolytic lesion in one rib which, at biopsy allegedly had proved to be a "simple cyst."

Cystic and cystlike lesions are seen in many other diseases. In *polyostotic fibrous dysplasia* proliferation of a hard fibrous tissue arranged in whorls and studded with immature bone spicules, sometimes also with islands of cartilage, leads to oval osteolytic lesions (PLATES 26*a*, *b* 27*a*) At x ray examination the pseudocystic lesions in polyostotic fibrous dysplasia can hardly be distinguished from cysts. These lesions are not true cysts, however because they do not contain fluid but only typical fibrous tissue. Since calcium and phosphorus values of serum and urine usually remain normal in this disease, the differentiation from hyperparathyroidism is easy In addition, the bone cortex between the cystlike lesions is normal, in contrast to the generalized resorption of bone which exists in most cases of Recklinghausen's bone disease. In polyostotic fibrous dysplasia a tendency to sclerosis of the bone exists which sometimes manifests itself in the form of a hyperostosis of the occipital squama of the calvarium (PLATE 28*b*) The cystlike lesions, too often show patchy sclerosis. Pigmented patches of the skin with ragged edges (PLATE 27*b*) and, in women, premature menarche are frequent signs of polyostotic fibrous dysplasia not found in Recklinghausen's bone disease.

Expanding osteolytic, sometimes even cyst

like lesions which erode or perforate through the cortex and lead to periosteal irritation, are often malignant and especially *sarcomatous* in nature. The irritation of the periosteum is commonly present in the form of extra-osseous vertical spicules extending into the soft tissues.

Cystlike osteolytic areas may be caused by a proliferation of reticulum or histiocytic cells, as occurs in *eosinophilic granuloma* (PLATE 22c), *Hand-Schüller-Christian's disease* (PLATE 22a), and *Letterer-Siwe's disease*.

Round osteolytic areas in the skull belong to the most characteristic manifestations of Hand-Schüller-Christian's disease. These lesions consist of a proliferation of reticulum cells or histiocytes which secondarily become infiltrated with cholesterol esters. The same lipoidgranuloma invades the orbits and the neighborhood of the sella turcica, causing exophthalmus, and diabetes insipidus or infantilism, respectively. Occasionally lipoid granulomas may involve other bones than the calvarium. These lesions in the bones of the extremities are also often round, osteolytic and have a cystlike appearance. However a lipoidgranuloma may also cause septate lesions that could be readily confused with a giant cell tumor. If the triad of multiple osteolytic cystlike lesions in the calvarium, diabetes insipidus, exophthalmus is present, the diagnosis of Hand-Schüller-Christian's disease or lipoidgranulomatosis can be considered certain. In some cases biopsy of the lesion will be necessary to establish the diagnosis.

Diffuse dissemination of submiliary foci of lipoidgranulomatosis is often found in the lungs. Since in Hand-Schüller-Christian's disease the early lesion consists only of histiocytic proliferation without lipoid deposition, some patients may request medical advice when a pure reticulum cell proliferation exists. In this early stage, large numbers of eosinophils are often present among the proliferating histiocytes. This initial stage of the disease is designated eosinophilic granuloma. In this lesion one, occasionally more, osteolytic areas, usually round or oval in shape (PLATE 22c) are found. The eosinophilic granulomas are localized mainly in the peripheral skeleton, but they also frequently occur in the skull.

Finally an acute stage of reticulum cell proliferation is known where the lesions are not limited to the bone but are also present in the skin and visceral organs. This acute form of the disease, which occurs primarily in infants and small children, is known as Letterer-Siwe's disease. In this form of histiocytosis, fever, anemia, loss of weight, together with an eczema like eruption and hemorrhagic tendency are the outstanding clinical signs. Most of these children die at a young age. Here, also round osteolytic areas, although prevalent in the skull, may also be found in the rest of the skeleton. The anemia, the skin eruption and the skeletal lesions are caused by a proliferation of histiocytes. In this way it becomes evident that Hand-Schüller-Christian's disease, eosinophilic granuloma and Letterer-Siwe's disease are different stages of the same disease, characterized by a proliferation of reticulum cells or histiocytes.

It is usually believed that in the border of the osteolytic lesions, due to one of these three histiocytic granulomas, no sclerosis is found. This rule has exceptions: we have occasionally encountered a *thin* osteosclerotic rim surrounding the osteolytic lesions due to any of these forms of histiocytosis.

In the skull, round osteolytic lesions caused by *epidermoid carcinoma* or cholesteatoma occur. These osteolytic areas are surrounded by a clear-cut sclerotic rim which shows marked scalloping (PLATE 22b). The tumors have a tendency to penetrate inward and may give rise to marked cerebral symptoms and signs.

Round, well circumscribed, punched-out osteolytic lesions may be caused by *plasmocytomas*. For the differential diagnosis it should be stressed again that plasmocytomas

origin (osteitis condensans ilei) is, fortunately a rare disease.

In the few patients with sickle cell anemia who live beyond the age of 40 years, the skeleton may ultimately become sclerotic. In young patients the proliferation of the bone marrow, present in all hemolytic anemias, leads to weakening of cortex and cancellous bone. In the lumbar spine, hourglass vertebrae may be present in the dorsal spine wedging of vertebral bodies results. Finally in older patients with sickle cell anemia, these hourglass vertebrae may become sclerotic (PLATE 29d)

CYSTS AND CYSTLIKE LESIONS

Simple bone cysts are usually roundish or oval osteolytic lesions with smooth contours. Although congenital bone cysts, so-called unicameral cysts, located in the metaphysis, are rather frequently encountered, most of the bone cysts are traumatic in nature and occur in nearly all diseases where generalized *bone resorption is present. A slight trauma,* which would not cause any changes in normal bone, may lead, via a hemorrhage, to cyst formation in debilitated bones.

In *Recklinghausen's bone disease* cysts frequently occur Recklinghausen even gave the name osteitis fibrosa cystica generalisata to the disease he described. Not all the cystic lesions observed in Recklinghausen's bone disease are actually cysts. Part of these so-called cysts in hyperparathyroidism are giant cell tumors or osteoclastomas (PLATES 8c 11a) Many giant cell tumors exhibit the well known typical septate appearance (PLATE 8b) but others present on the x rays as simple cysts (PLATES 8c 11a) Osteoclastomas rapidly ossify after the parathyroid adenomas have been removed, whereas true cysts persist in an unchanged condition after the operation.

In the presence of a cystic lesion of the skeleton, the possibility of an osteoclastoma due to hyperparathyroidism must always be considered. In each case a careful investigation of the calcium and phosphorus metabolism is in order The biochemical characteristics of hyperparathyroidism have been repeatedly mentioned (p. 65) This investigation is also necessary when only one cyst is found in the presence of a completely normal x ray appearance of the rest of the skeleton. Long before the resorption of bone has gone so far that the loss of bone substance can be visualized by x ray examination, the solidity of the skeleton has already suffered and a tendency to the formation of traumatic bone cysts exists. A good example of this is the patient with hyperparathyroidism and pseudo-diabetes insipidus mentioned before (p. 79) where the only bone lesion ever discovered was limited to one osteolytic lesion in one rib which, at biopsy allegedly had proved to be a "simple cyst."

Cystic and cystlike lesions are seen in many other diseases. In *polyostotic fibrous dysplasia* proliferation of a hard fibrous tissue arranged in whorls and studded with immature bone spicules, sometimes also with islands of cartilage, leads to oval osteolytic lesions (PLATES 26a, b, 27a) At x ray examination the pseudocystic lesions in polyostotic fibrous dysplasia can hardly be distinguished from cysts. These lesions are not true cysts, however because they do not contain fluid, but only typical fibrous tissue. Since calcium and phosphorus values of serum and urine usually remain normal in this disease, the differentiation from hyperparathyroidism is easy In addition, the bone cortex between the cystlike lesions is normal in contrast to the generalized resorption of bone which exists in most cases of Recklinghausen's bone disease. In polyostotic fibrous dysplasia a tendency to sclerosis of the bone exists which sometimes manifests itself in the form of a hyperostosis of the occipital squama of the calvarium (PLATE 28b) The cystlike lesions, too, often show patchy sclerosis. Pigmented patches of the skin with ragged edges (PLATE 27b) and, in women, premature menarche are frequent signs of polyostotic fibrous dysplasia not found in Recklinghausen's bone disease.

Expanding osteolytic, sometimes even cyst

like lesions which erode or perforate through the cortex and lead to periosteal irritation, are often malignant and especially *sarcomatous* in nature. The irritation of the periosteum is commonly present in the form of extra-osseous vertical spicules extending into the soft tissues.

Cystlike osteolytic areas may be caused by a proliferation of reticulum or histiocytic cells, as occurs in *eosinophilic granuloma* (PLATE 22*c*), *Hand-Schüller-Christian's disease* (PLATE 22*a*), and *Letterer-Siwe's disease*

Round osteolytic areas in the skull belong to the most characteristic manifestations of Hand-Schüller-Christian's disease. These lesions consist of a proliferation of reticulum cells or histiocytes which secondarily become infiltrated with cholesterol esters. The same lipoidgranuloma invades the orbits and the neighborhood of the sella turcica, causing exophthalmus, and diabetes insipidus or infantilism, respectively Occasionally, lipoid granulomas may involve other bones than the calvarium. These lesions in the bones of the extremities are also often round, osteolytic and have a cystlike appearance. However a lipoidgranuloma may also cause septate lesions that could be readily confused with a giant cell tumor If the triad of multiple osteolytic cystlike lesions in the calvarium, diabetes insipidus, exophthalmus is present, the diagnosis of Hand-Schüller-Christian's disease or lipoidgranulomatosis can be considered certain. In some cases biopsy of the lesion will be necessary to establish the diagnosis.

Diffuse dissemination of submiliary foci of lipoidgranulomatosis is often found in the lungs. Since in Hand-Schüller-Christian's disease the early lesion consists only of histiocytic proliferation without lipoid deposition, some patients may request medical advice when a pure reticulum cell proliferation exists. In this early stage, large numbers of eosinophils are often present among the proliferating histiocytes. This initial stage of the disease is designated eosinophilic granuloma. In this lesion one, occasionally more, osteolytic areas, usually round or oval in shape (PLATE 22*c*) are found. The eosinophilic granulomas are localized mainly in the peripheral skeleton, but they also frequently occur in the skull.

Finally, an acute stage of reticulum cell proliferation is known where the lesions are not limited to the bone but are also present in the skin and visceral organs. This acute form of the disease, which occurs primarily in infants and small children, is known as Letterer-Siwe's disease. In this form of histiocytosis, fever, anemia, loss of weight, together with an eczema-like eruption and hemorrhagic tendency, are the outstanding clinical signs. Most of these children die at a young age. Here, also round osteolytic areas, although prevalent in the skull, may also be found in the rest of the skeleton. The anemia, the skin eruption and the skeletal lesions are caused by a proliferation of histiocytes. In this way it becomes evident that Hand-Schüller-Christian's disease, eosinophilic granuloma and Letterer-Siwe's disease are different stages of the same disease characterized by a proliferation of reticulum cells or histiocytes.

It is usually believed that in the border of the osteolytic lesions, due to one of these three histiocytic granulomas, no sclerosis is found. This rule has exceptions we have occasionally encountered a *thin* osteosclerotic rim surrounding the osteolytic lesions due to any of these forms of histiocytosis.

In the skull, round osteolytic lesions caused by *epidermoid carcinoma* or cholesteatoma occur These osteolytic areas are surrounded by a clear-cut sclerotic rim which shows marked scalloping (PLATE 22*b*) The tumors have a tendency to penetrate inward and may give rise to marked cerebral symptoms and signs.

Round, well circumscribed, punched-out osteolytic lesions may be caused by *plasmocytomas* For the differential diagnosis it should be stressed again that plasmocytomas

are purely osteolytic in character never cause any bone proliferation and therefore are never surrounded by a sclerotic ring (PLATE 36*a*)

Mostly in the skull, but also other parts of the skeleton, *lymphomatous* disease (PLATES 31*a* 33*a* 37*c*) may cause round, punched-out lesions which, roentgenologically at least, may be very similar to multiple plasmocytomas. Such cystlike lesions may also stem from *metastases of a malignant tumor* (PLATE 46*c*) The skeletal manifestations in particular of thyroid malignancies frequently exhibit a cystlike configuration (PLATE 45*d*) Unless the presence of a primary carcinoma can be ascertained, or diagnostic signs of a lymphoma can be found, the diagnosis of these round circumscribed bone defects will usually depend upon the biopsy of such lesions.

Precipitations of uric acid within the bone and cartilage—so-called tophi—are pathognomonic of *gout* On the x rays these tophi present as osteolytic lesions, because the bone substance has been replaced by uric acid (PLATE 38*c*) Although these small, round, cystlike lesions are most frequently found near the first metatarso-phalangeal joint, tophi may also be present in any other part of the skeleton (PLATE 38*a* *b* *d* *e*) In severe and chronic cases of gout, large irregular osteolytic areas may be encountered which occasionally lead to the erroneous diagnosis of a bone sarcoma. In the absence of the classical pain attacks in the first metatarso-phalangeal joint (podagra) palpable tophi in the cartilage of the ears and/or a high uric acid content of the serum usually allow for the correct diagnosis. Microscopically the contents of a tophus consist of numerous white needle-like crystals which can easily be identified as uric acid by the murexide reaction (p 169)

It must be added that small cystlike osteolytic areas are often found in the neighborhood of joints involved in *rheumatoid arthritis*

In *Paget's disease* pseudocysts are sometimes visualized among the other bone lesions characteristic for this disease (PLATE 19*e*) These osteolytic areas represent cavities filled with fatty tissue.

In *Boeck's sarcoidosis* small cystic areas, mainly localized in the phalanges, are found (PLATE 13*b*) The content of the cystic lesions in Boeck's sarcoidosis consists of granulomatous masses that histologically resemble tuberculous tubercles. This histologic picture is the reason that Jüngling originally described the disease under the name "osteitis tuberculosa cystoides." This name has become obsolete since the tuberculous etiology of Boeck's sarcoidosis is no longer accepted. In Boeck's sarcoids, no tubercle bacilli can be found and caseation and calcification do not occur Whereas the visceral lesions of Boeck's sarcoidosis occur very frequently in many areas of the United States, especially in the South, bone lesions are decidedly rare in this country In Boeck's sarcoidosis the cystlike changes in the phalanges occur mainly in the presence of skin lesions of the fingers—so-called chillblain lupus. In the rare cases where the skin over the fingers is normal but cystlike bone lesions are present, the diagnosis can be made only if lymph node swelling or other signs of Boeck's sarcoids can be found. If necessary a liver puncture, a biopsy of a peripheral or a scalenus lymph node, or a Nickerson-Kveim test should be performed.

In the adult form of acute *leukemia* small round osteolytic lesions due to the proliferation of leukemic cells are frequently encountered. These lesions may occur in any part of the skeleton, but are especially frequent in the neck of the femurs and the scapulae.

Infectious processes may cause osteolytic lesions. Since the clinical picture of osteomyelitis due to staphylococci has changed completely with the advent of antibiotics, the so-called Brodie abscesses have become rarities. These Brodie abscesses were sequelae of osteomyelitis and presented as round osteolytic lesions, filled with pus and surrounded by markedly sclerotic bone.

ON SEPTATE OSTEOLYTIC LESIONS

In all cases where an osteolytic lesion is

traversed by multiple bone septa, the possibility of a *giant cell tumor* (*osteoclastoma*) should come to mind. In this connection several points merit special consideration. Giant cell tumors, unless developing in patients with *Recklinghausen's bone disease,* are frequently malignant. Notwithstanding contrary statements in the literature, these tumors are not traumatic in origin. Although the great majority of the osteoclastomas are independent tumors, the presence of a giant cell tumor must always raise the possibility of hyperparathyroidism. Every patient in whom a giant cell tumor is found deserves a careful investigation of the calcium and phosphorus of the serum and urine, and a determination of the alkaline phosphatase of the serum to exclude a metabolic disorder. This especially holds true for giant cell tumors located in the skull, whether it be the calvarium, the maxilla or the mandible (PLATE 11*a*). In this location, giant cell tumors are usually a manifestation of Recklinghausen's disease. Many cases of early hyperparathyroidism exist where, save for the presence of one or more giant cell tumors in the calvarium or jaw, the skeleton appears normal at the x-ray examination. This is one exception to Recklinghausen's statement that in the bone disease which carries his name, the skeleton in its entirety is involved by generalized fibrous osteitis.

Osteoclastomas may or may not be septate in structure. PLATES 8*c* and 11*a* are examples of a purely osteolytic nonseptate giant cell tumor in hyperparathyroidism. This makes the differential diagnosis between a simple bone cyst and an osteoclastoma extremely difficult, since both lesions may occur in hyperparathyroidism. It has already been mentioned that after successful removal of the parathyroid adenoma such differentiation is usually easy. The recalcification of the osteoclastomas takes places very readily whereas the bone cysts remain unchanged for many months or even years.

Unfortunately, it is very difficult to differentiate histologically between a giant cell tumor of unknown origin and an osteoclastoma due to hyperparathyroidism. Giant cell tumors, unassociated with parathyroid disease, rarely occur in patients below 20 or above 40 years of age. They usually start in the metaphysis and spread into the epiphysis. Their most common localization is in the long bones, especially in the neighborhood of the knee joint, although they are also but less frequently, found in other long bones and in flat bones. On the other hand, an osteolytic lesion containing many bone septa is by no means always a giant cell tumor. In all septate osteolytic lesions, especially if present in one of the less frequent locations, the possibility of a lesion other than a giant cell tumor must be considered. Large, septate, osteolytic lesions in the iliac bone are very frequently caused by the presence of *plasmocytomas* (PLATE 35*b*). Since plasmocytomas hardly ever cause a periosteal reaction, the presence of periostitis over a septate lesion, regardless of its location, strongly militates against the diagnosis of plasmocytoma. In general, a biopsy of every septate lesion is necessary. If, in a patient with an osteolytic septate lesion, Bence Jones protein in the urine and/or hyperglobulinemia are found, the diagnosis of a plasmocytoma is certain and will easily be confirmed by a bone marrow puncture and electrophoresis.

Less frequently, other bone lesions present an x-ray picture that may resemble a giant cell tumor. In this connection, *lipoidgranulomas, lymphomas, metastases of neoplasms especially of clear cell carcinomas of the kidney,* occasionally even *chondromas* and *fibrous dysplasia* (PLATE 23*d*) must be mentioned.

Finally, a few words about the *aneurysmal bone cysts* must be added. Aneurysmal bone cysts, usually localized in long bones and spine, occur mainly in children and young adults. The radiologic aspect of this lesion is commonly described as being comparable to an "expanded blood-filled sponge." In certain instances these features may be reminiscent of a giant cell tumor.

ON THE EPIPHYSEAL DISK

During the years of childhood the cartilage

of the epiphyseal disks is gradually replaced by bone. This enchondral ossification proceeds systematically and the disappearance of the epiphyseal disks of each bone takes place at a special age. One of the last epiphyseal disks to disappear is the one which separates the iliac crest from the iliac bone. X rays of the pelvis reveal that this disk remains open until the 18th or 20th year

The vast majority of chronic diseases of childhood lead to retardation of the closure of the epiphyseal disks and thereby to some degree of dwarfism. Thus, in infantilism, whether of cardiac, intestinal, renal or any other origin open epiphyseal disks are always found.

In true rickets not only a delay in closure of the disks, but also swelling of the cartilage of the disk is found. The abnormal proliferation of the cartilage situated near the metaphyseal end of the disk causes the so-called cupping of the metaphysis typical of rickets (PLATE 3a c d) Rickets in children and osteomalacia in adults develop when a normal amount of bone matrix is manufactured, but no calcium and/or phosphorus are available for the ossification process. Thus, rickets occurs in avitaminosis D due to the impaired absorption of calcium from the intestine. In this disease the intestinal absorption of phosphorus is, however, normal. Avitaminosis D may be caused by lack of vitamin D in the food combined with lack of exposure to sunshine, or by fatty diarrhea which leads to considerable losses of fat soluble vitamin D in the stool by excessive excretion of phosphate in the urine, caused by lack of reabsorption of phosphates in the proximal tubules (Lignac Fanconi's syndrome and phosphate diabetes) or by excessive losses of calcium in the urine, caused by impairment of ammonia and acid formation in the distal tubules (hyperchloremic tubular acidosis)

Specific symptoms and signs originate when the reabsorption of phosphates, glucose and amino acids is impaired in the proximal tubules All three substances then appear in abnormally large quantities in the urine. In this disease (which carries different names but which should be designated Lignac Fanconi's syndrome) the loss of large amounts of phosphates in the urine leads to hypophosphatemia.

Although serum calcium may remain normal, the calcium phosphate formation is inhibited in the absence of phosphates, and calcification of the epiphyseal disks cannot take place. On the x-rays, open epiphyseal disks are seen, just as is the case in rickets due to avitaminosis D In such children renal glucosuria and aminoaciduria frequently occur It should be added that many of the children are suffering from the deposition of crystalline cystine in many organs, so that cystinosis is a frequent, though not a constant occurrence in this syndrome. Occasionally patients are encountered where only the reabsorption of phosphate, not of glucose or amino acids, is impaired. In the ensuing syndrome, which has been designated by Fanconi as phosphate diabetes, the same bone anomalies do occur

Rickets and osteomalacia also occur in lesions of the distal convoluted tubules. The ensuing hyperchloremic tubular acidosis leads to marked losses of calcium and other cations. Calcification is disturbed and vitamin D-resistant rickets and osteomalacia develop.

In long-standing chronic renal insufficiency in childhood, delay of the closure of the epiphyseal disks occurs. In all cases of chronic glomerulonephritis, vascular diseases of the kidneys, pyelonephritis, congenital anomalies, tuberculosis, amyloid, etc., uremia develops because the glomeruli are gradually replaced by fibrous scar tissue. The bone lesions that occur in uremia due to glomerular damage must be distinguished from the bone lesions due to tubular dysfunction, mentioned in the previous paragraphs. When the blood urea nitrogen, creatinine, uric acid, inorganic phosphorus, sulphate, and organic acids of the serum are markedly increased for a long time, chronic acidosis causes generalized resorption of bone followed by osteitis fibrosa. This explains the names renal osteitis fibrosa, renal osteofibrosis or renal

osteopathy Although in this condition the epiphyseal disks remain open, this uremic osteopathy should under no condition be identified with rachitic bone lesions.

The differential diagnosis between uremic osteitis fibrosa and hyperparathyroidism has been discussed on page 92. In contrast to the changes of the epiphyseal disks in rickets, in renal osteofibrosis the metaphyseal plate of the epiphysis is completely disorganized and a so-called woolly appearance of the disk results. Often the metaphysis crumbles and the intact diaphysis penetrates the weakened epiphysis (PLATE 12a b) Subperiosteal resorption of bone is found, especially in the phalanges and often also in other parts of the skeleton. Even large doses of vitamin D have no influence upon the uremic bone lesions (see footnote, p. 89) When skeletal anomalies develop in chronic uremia, the prognosis is always very serious. Thus, although delay of closure of the epiphyseal disk exists in both rickets and chronic uremia, these diseases can be distinguished roentgenologically

ON THE INTERVERTEBRAL DISK

There exists a general rule that in inflammatory diseases of segments of the vertebral column the intervertebral disks are destroyed, causing the involved vertebral bodies to coalesce into one large block of bone. At the same time, the inflammatory granulation tissue and exudate spread into the paravertebral space and can be visualized as a paravertebral shadow

Destruction of the intervertebral disk is the first radiologic sign of an inflammatory disease of a vertebra. Since tuberculous spondylitis fortunately has become a rarity in this country the bulk of the inflammatory diseases of the spine are caused by salmonella (PLATE 48d), brucella and staphylococcus infections. The intervertebral disk also disappears when a vertebra is eroded by a syphilitic aneurysm.

Contrariwise, in tumors (PLATE 46b) lymphomas (PLATE 31b c) and myelomas (PLATES 2b 36a) of the spine, the vertical diameter of the affected vertebra may decrease until a complete collapse results, but the intervertebral disk as a rule remains intact. At the same time, a paravertebral swelling hardly ever develops. The same holds true in osteoporosis as seen in the postmenopausal period (PLATES 1a, 2a), in senility, in Gaucher's disease (PLATE 1b), in osteomalacia (PLATE 5b), lipoid and eosinophilic granuloma (PLATE 23a, b c), leukemia and hemolytic anemia (PLATE 30a) The intervertebral disk is also unchanged in traumatic fractures of the vertebral bodies.

No rule is free from exceptions. In certain inflammatory conditions, i.e., fungus disease, especially actinomycosis and blastomycosis of the spine, the vertebral bodies may show extensive involvement, but the intervertebral disks often remain normal. The reverse is also true. There are rare cases of multiple myeloma—especially in older people—where after a vertebral collapse, the intervertebral disk disappears (PLATE 36b) and a paravertebral shadow is formed. All these deviations from the general rule are very rare and on the whole the differences in changes of the vertebral disk occurring in inflammatory and noninflammatory disease of the spine, as mentioned in the previous paragraphs, can be used as reliable differential diagnostic directives.

The most extreme instance of vertebral collapse with intact intervertebral disks is found in eosinophilic and/or lipoidgranuloma of the spine. In this disease, the collapse of the vertebral body may be so extreme that only a paper thin layer of bone, a so-called "biscuit" vertebra, remains (PLATE 23c) The intervertebral disks, however remain unchanged. It has gradually become apparent that the remarkable roentgen picture which results is identical to the changes observed in the vertebrae planae described by Calvé. Vertebrae planae occur mainly in children between 2 and 12 years old. The pains in the back, limitation of mobility of the spine and gibbus formation led, in most cases, to the presumptive diagnosis of tuberculous spondylitis until at roentgen examina

tion the biscuit vertebra with intact intervertebral disks was discovered. The collapse of the vertebral body was progressive, even if the child was completely immobilized. The etiology of this disease remained a mystery for many decades. Recently, however, it has been realized that the vertebrae planae of Calvé are usually, perhaps always, caused by an eosinophilic granuloma.

The special changes of the intervertebral disks that occur when the vertebral column is weakened by a general resorption of bone have already been discussed on p. 202 of this chapter. Here we will mention only the formation of Schmorl's nodules (PLATE 1c), the wedging of the bodies of the thoracic vertebrae (PLATE 2a) and the formation of hourglass or fish vertebrae in the lumbar spine (PLATE 1a).

ON PERIOSTITIS

Periosteal bone formation is found in many different diseases. In olden times when *syphilis* was a frequent disease, syphilitic periostitis, producing severe pains especially during the night, was a common occurrence. Periostitic bone formation was also often seen in *extensive rickets* in infants, but the disease has become a rarity today. The same holds true of the elevation of the periosteum due to subperiosteal hemorrhage, a characteristic finding in *scurvy*.

Periostitis is rather frequently observed as a complication of *Paget's disease*. As a matter of fact, periostitic bone formation is one of the factors which contributes to the thickening of the diameter of the cortex of the Paget bone, a typical manifestation of osteitis deformans.

Periostitis is an integral part of the syndrome of *hypertrophic osteoarthropathy* (PLATE 44a). In this syndrome, clubbing of the fingers, painful swelling of the distal ends of the extremities and subacute arthritis are the foremost signs. The painful swelling of the extremities is due to an ossifying periostitis. Unfortunately because of the swelling of the joints, hypertrophic osteoarthropathy is often erroneously diagnosed as subacute rheumatoid arthritis. In such cases the presence of clubbing of the fingers always points to the presence of a hypertrophic osteoarthropathy which can be easily confirmed by an x-ray of the painful joints.

Hypertrophic osteoarthropathy develops in the course of chronic lung disease, especially in primary carcinoma of the lung. It is also found in chronic bronchiectasis, chronic lung abscess, chronic empyema of the pleura and endothelial tumors of the pleura. Hypertrophic osteoarthropathy however is not limited to pulmonary diseases, being also present in subacute bacterial endocarditis, congenital lesions of the heart with cyanosis, ulcerative colitis, regional enteritis, nontropical sprue, pulmonary localizations of Hodgkin's disease, and liver cirrhosis. Thus, the presence of periostitis of the distal parts of the extremities is always a reason to carefully investigate many different diagnostic possibilities. It must be emphasized that occasionally the clubbing of fingers, pains and joint swelling due to hypertrophic osteoarthropathy may precede the symptoms and signs of the underlying disease. This is especially true for primary lung cancer.

In *acute leukemia* in children, the proliferation of leukemic tissue frequently invades the subperiosteal space. This then leads to an elevation of the periosteum which can often be visualized on x-ray films (PLATE 30b). Here, again, this irritation of the periosteum may lead to painful swelling of the terminal ends of the extremities and adjoining joints. As a result, children with subacute leukemia are often erroneously diagnosed as suffering from rheumatoid arthritis.

The differential diagnosis between hypertrophic osteoarthropathy and acute leukemia is usually easy. Acute leukemia causes bone lesions practically only in children, whereas bronchogenic cancer and the other diseases leading to hypertrophic osteoarthropathy are mainly present in adults. A blood smear and a bone marrow puncture will immediately solve this differential diagnostic problem. In this connection it may be mentioned that

calcium deposition in and near the joints, which occurs in renal osteitis fibrosa (PLATES 12c 13a), hyperparathyroidism, Burnett's syndrome (PLATE 13c, d), and hypervitaminosis D (PLATE 4b), may also cause swelling and redness of the joints. It follows that the diagnosis of acute rheumatoid arthritis should never be made without a careful differential diagnosis.

Every bacterial or fungal infection of bone can lead to a reactive ossifying periostitis, more in children than in adults. This is especially marked in *actinomycosis* and *blastomycosis* of the skeleton. Even when the osseous infection has already improved considerably the wide shell of new periosteal bone formed under influence of the bacterial or fungal osteitis may still be present. The bone bridges that are a frequent occurrence in chronic osteomyelitis of the spine due to *typhoid salmonella, staphylococcus infection* and *brucella*, are also manifestations of periosteal bone formation under the influence of a chronic infection. This phenomenon is less marked in chronic tuberculosis of the spine.

Ossifying periostitis must be distinguished from *cortical hyperostosis*. Excessive new formation of cortical bone takes place in children with *hypervitaminosis A* (PLATE 7b c) A comparable cortical hyperostosis occurs in children without a known cause. This disease, first described by Caffey as *infantile cortical hyperostosis* (PLATE 6b), usually involves the mandible (PLATE 6e) In contrast, the mandible remains unchanged in hypervitaminosis A. In the latter hyperostosis around the metatarsals is frequent, a localization rare in cortical hyperostosis. Infantile cortical hyperostosis always involves the entirety of the bone (PLATE 6c d), which is not the case in hypervitaminosis A (PLATE 7c) The latter disease never develops before the children have reached the age of two years, whereas Caffey's disease occurs in children under six months. Needless to say, in hypervitaminosis A an excessive intake of this vitamin must have taken place, the vitamin A content of the serum must be abnormally high and the bone lesions must disappear readily after cessation of the vitamin A influence.

BIOCHEMICAL DIFFERENTIATION OF BONE LESIONS

No changes in calcium and phosphorus metabolism are found in the following conditions

(1) Postmenopausal and senile osteoporosis (except for a slight increase in the inorganic serum phosphorus)

(2) Osteoporosis due to Cushing's syndrome.

(3) Scurvy

(4) Hypervitaminosis A. In this disease the vitamin A content of the serum is very high.

(5) Infantile cortical hyperostosis.

(6) Hand-Schüller-Christian's disease.

(7) Letterer-Siwe's disease.

(8) Eosinophilic granuloma.

(9) Polyostotic fibrous dysplasia. Occasionally an increase of the alkaline phosphatase is found when marked sclerosis of the lesions sets in. The same happens when multiple fractures are present in the process of healing

(10) Hemolytic anemias.

(11) Lymphomas and leukemias (except in rapidly destructive cases) In addition, the uric acid content of the blood is high in leukemias and may increase after roentgen ray treatment of lymphomas.

(12) Gout. In the vast majority of cases the uric acid content of the blood serum is increased.

(13) Gaucher's disease. Recently an increase of the acid phosphatase of the serum has been found.

(14) Albers-Schönberg's disease. In this disease, too, a high acid phosphatase has been reported.

(15) Neurofibromatosis. When as is occasionally the case, a tubular dysfunction coexists with the neurofibromatosis, hypophos-

ondary uremia is most probable. When, in such patients, osteoclastomas are present, the diagnosis of hyperparathyroidism is mandatory. For the other differential diagnostic considerations see page 92.

As mentioned above, the presence of hypophosphatemia is a very important point for the diagnosis of hyperparathyroidism. Aside from this condition hypophosphatemia occurs only in avitaminosis D and in tubular dysfunction. In contrast to hyperparathyroidism, in the latter two conditions hypercalcemia is not found. In all other diseases with hypercalcemia the phosphorus content of the serum does not decrease. Therefore, if not only hypercalcemia but also hypophosphatemia are present in a patient with Burnett's syndrome, hypervitaminosis D or Boeck's sarcoidosis, the presence of a coexisting hyperparathyroidism must seriously be considered. Autopsies of patients with Burnett's syndrome have been reported where it was proved that they were suffering from hyperparathyroidism. This might perhaps have been avoided if the phosphorus content of the serum had been more carefully scrutinized. On page 102 the observation is reported of a boy with Boeck's sarcoidosis, proved by histologic examination of several biopsies, who had continuously hypercalcemia combined with a serum phosphorus below 3 milligrams per cent. At operation a parathyroid adenoma was found. In this case the diagnosis was relatively simple because the patient's identical twin brother had been operated on a few years previously for hyperparathyroidism.

Special mention should be made of hypercalcemia, which is present in rapidly destructive bone diseases, mainly in widespread cancer metastases and in multiple myeloma, but also occasionally in lymphomatous diseases.

The exact role alkaline phosphatase plays in the ossification process has not been elucidated in all details. However, it cannot be doubted that this enzyme must be of great importance for the deposition of bone substance (p. 7). Alkaline phosphatase is formed by osteoblasts, and in many cases of osteoblastic hyperactivity an excess of alkaline phosphatase is produced, causing an elevation of the alkaline phosphatase of the serum. It must be added that an increase of the alkaline phosphatase of the blood also occurs in obstructive jaundice and often in nonjaundiced patients with liver damage. The latter rise of the alkaline phosphatase in the blood is connected with the fact that alkaline phosphatase is manufactured within the cells of the walls of the cholangioles. Thus, proliferation of the bile ductules, a frequent occurrence in many different kinds of liver disease, causes an increase of the alkaline phosphatase of the blood, even if no jaundice exists.

All this emphasizes that an increase of the alkaline phosphatase is far from pathognomonic for an increase of the activity of osteoblasts.

As far as the bone diseases are concerned, in hyperparathyroidism with extensive bone lesions (i.e., in Recklinghausen's bone disease) the alkaline phosphatase of the serum always increases. The latter biochemical change occurs because in Recklinghausen's bone disease destruction of bone and reconstruction of bone are both markedly increased. It has already been mentioned that in patients with generalized resorption of bone, the diagnosis of Recklinghausen's bone disease is highly improbable when no increase of alkaline phosphatase of the serum is present.

It may also be repeated that when hyperparathyroidism has led to nephrolithiasis, gastrointestinal lesions or another characteristic syndrome *without* clear-cut bone lesions, the alkaline phosphatase of the serum remains normal.

High alkaline phosphatase will always be found in the serum of patients wtih extensive Paget's disease. The alkaline phosphatase remains normal in monostotic Paget's disease.

The reconstruction of bone that always takes place in rickets, osteomalacia, and renal osteitis fibrosa is the cause of the increase

of the alkaline phosphatase—which is a constant finding in these diseases.

In Boeck's sarcoidosis, hypercalcemia is a frequent finding, but the serum phosphorus usually remains normal. An increase of the alkaline phosphatase of the serum does occur, though much more rarely than hypercalcemia. The anomalies of the calcium metabolism in Boeck's sarcoidosis are partly comparable to the metabolic changes found in hypervitaminosis D. Though in the latter disease no increase of the alkaline phosphatase is found, it has been frequently surmised that the hypercalcemia of patients with Boeck's sarcoidosis could be caused by the formation of vitamin D–like substances.

In certain forms of osteosclerosis where osteoblastic hyperactivity *must* be present, no increase of the alkaline phosphatase of the serum can be found. In osteoblastic metastatic malignancies and in osteosclerosis due to Hodgkin's disease and other lesions, the alkaline phosphatase may or may not be increased. In such patients it is always difficult to decide whether an increase of this enzyme in the serum is due to proliferation of osteoblasts caused by the skeletal lesion, or due to the liver involvement so common in these diseases.

Even in widespread osteosclerosis, as found in aleukemic megakaryocytic myelosis, the alkaline phosphatase of the serum is not always increased. In polyostotic fibrous dysplasia and in lipoidgranulomatosis, the alkaline phosphatase of the serum may be increased if in the later stages of the disease, sclerosis of the skeleton develops.

The alkaline phosphatase of the serum is not increased in Albers-Schönberg's disease and in fluoride poisoning. These diseases may well be due mainly to decreased osteoclasia and not to increased osteoblastic action.

In multiple myeloma, a purely osteolytic process without any increase of reactive bone repair, the alkaline phosphatase remains within normal limits. This statement must be qualified because many patients with multiple myeloma are treated with urethane. The latter medicament, if given over a long period of time, may cause liver degeneration, and urethane treatment must occasionally be stopped because the patient develops jaundice or hepatosplenomegaly. If, under influence of urethane, the liver function deteriorates, the alkaline phosphatase of the serum may increase even if no jaundice develops.

In the prostate a special phosphatase is manufactured which has its greatest activity at an acid pH. Under normal conditions this acid phosphatase remains within the prostate and only traces appear in the blood. However, when a carcinoma of the prostate develops, the acid phosphatase of the serum usually increases above the maximum normal level of 0.8 Bodansky unit or 4 King Armstrong units per 100 cc. of blood. This is especially the case when the tumor has penetrated the capsule of the gland and skeletal metastases have formed. Under the influence of estrogen treatment or orchidectomy the acid phosphatase often returns to normal levels.

It must be added that any condition in which the alkaline phosphatase is considerably increased may lead to a secondary increase of acid phosphatase. The latter phenomenon is without any special clinical significance. When the alkaline phosphatase content of the blood has risen to high levels in Paget's disease, liver disease, Recklinghausen's bone disease, etc., an increase of the acid phosphatase does not indicate the presence of a prostatic carcinoma. The possibility that the rise in acid phosphatase could be due to Albers-Schönberg's disease or to Gaucher's disease always merits consideration.

ON METASTATIC CALCIFICATION

Metastatic calcification is a dangerous complication of the following conditions:

(1) Hyperparathyroidism.
(2) Renal disease in young individuals

leading to long-standing acidosis.

(3) Administration of excessive amounts of vitamin D

(4) Excessive ingestion of alkali and milk in patients with peptic ulcer (Burnett's syndrome)

(5) Alkalosis caused by long-standing vomiting in obstruction of the upper gastrointestinal tract.

(6) Chronic lower nephron dysfunction or so-called tubular acidosis.

(7) Rapidly destructive osteolytic bone lesions due to metastatic malignancies, multiple myeloma or Hodgkin's disease of the skeleton.

(8) Boeck's sarcoidosis.

(9) Sudden complete immobilization.

In all these conditions metastatic calcification of the kidneys, so-called nephrocalcinosis, occurs. Furthermore, in the first four conditions, metastatic calcification of the other visceral organs and of the subcutis is more prevalent than in the last five syndromes.

In skeletal metastases in patients with mammary cancer the tendency to metastatic calcification is considerably increased by the administration of testosterone, which is frequently used for therapeutic purposes.

The roentgenologic picture of nephrocalcinosis in all of these nine conditions is identical. The calcium deposits can be visualized only in the marrow of the kidney outlining the pelvis and surrounding the calyces (PLATE 6a) On the x ray the cortex is free of calcium, although the latter may be found at histologic examination.

TABLE 5

METASTATIC CALCIFICATION

	Serum Ca	*Serum P*	*Alk. Phosph.*	*Ca Urine*
Immobilization	High	Increased	Normal	High
Hyperparathyroidism	High	Decreased	High	High
Hypoparathyroidism	Low	High	Normal	Low
Uremia with acidosis	Low	High	Normal or Increased	Low
Burnett's Syndrome	High	Increased	Normal	Normal
Tubular Acidosis	Low	Normal or Decreased	High	High
Hypervitaminosis D	High	Increased	Normal	High
Malignant Osteolytic bone lesions	High	Increased	Increased or Normal	High
Boeck's Sarcoidosis	High	Normal	Normal or Increased	High

Clinical analysis indicates that different mechanisms must play a role in the causation of metastatic calcification. In hypervitaminosis D hyperparathyroidism, complete immobilization of young individuals, ulcer patients treated with alkali and calcium ingestion, Boeck's sarcoidosis and in widespread osteolytic metastatic disease of the skeleton, metastatic calcification is generally accompanied by hypercalcemia. When, however abnormal calcium deposition in the tissues occurs in young individuals with long-standing renal insufficiency and acidosis, a decrease of the calcium content of the serum is commonly found. Hypocalcemia also occurs commonly in nephrocalcinosis due to hyperchloremic tubular acidosis.

The levels of the inorganic phosphorus of the serum also vary in different forms of metastatic calcification. In renal insufficiency there is hyperphosphatemia, but in chronic hyperparathyroidism the serum phosphates

are decreased. Even the pH of the urine is unreliable as a criterium for the prediction of nephrocalcinosis. Acid urine is excreted in young individuals suffering from chronic uremia but in hyperparathyroidism and chronic tubular acidosis an alkaline urine is produced. Thus, metastatic calcification can occur (Table 2)

(1) In the presence of high serum calcium and slightly or moderately increased inorganic phosphate (hypervitaminosis D rapidly spreading skeletal malignancies, long standing treatment of ulcers with alkali and milk, immobilization, Boeck's sarcoids)

(2) In the presence of hypocalcemia and hyperphosphatemia (chronic uremia, hypoparathyroidism), or

(3) In the presence of hypercalcemia and hypophosphatemia (hyperparathyroidism)

This makes it difficult to explain metastatic calcification by over saturation of the tissue fluids with calcium phosphate local conditions of the tissues in which the calcium will be deposited must certainly play an important role.

In general, it can be said that deposition of calcium is prevalent in organs where the excretion of acid results in a temporary tissue alkalosis. Such an alkalosis would favor the precipitation of calcium phosphate and calcium carbonate. This would explain why metastatic calcification is so frequently seen in the kidneys, where acid phosphates are excreted in the stomach, where hydrochloric acid is produced and in the lungs, where carbon dioxide is removed. On the other hand, this explanation cannot be applied generally because in the heart muscle and in the subcutaneous tissue, calcinosis is also frequently observed. It may be repeated that in chronic uremia in young individuals, deposition of calcium salts in or near the synovial capsule of the joints gives rise to symptoms and signs which are often mistaken for rheumatoid arthritis.

Age plays an important role in some forms of metastatic calcification. In chronic uremia and also in immobilization, deposition of calcium in soft tissues seldom occurs except in young individuals. However, in the higher age groups, metastatic calcification is often caused by hyperparathyroidism or widespread skeletal malignancy

Finally, the condition of the kidney should be considered. Hypercalcemia and metastatic calcification due to rapidly spreading malignancies of the skeleton mainly occur if preexisting renal damage has been present. The latter also holds true for the cases of metastatic calcification after excessive ingestion of alkali and milk in ulcer patients. Needless to say that 70 per cent of the myeloma patients have damaged kidney function, due to the excretion of Bence Jones protein or other myeloma proteins.

In all conditions where the serum calcium reaches a value of 17 milligrams per cent or higher symptoms and signs of the hypercalcemic syndrome develop. Fatigue, headache, drowsiness, obstipation are the outstanding features of this condition.

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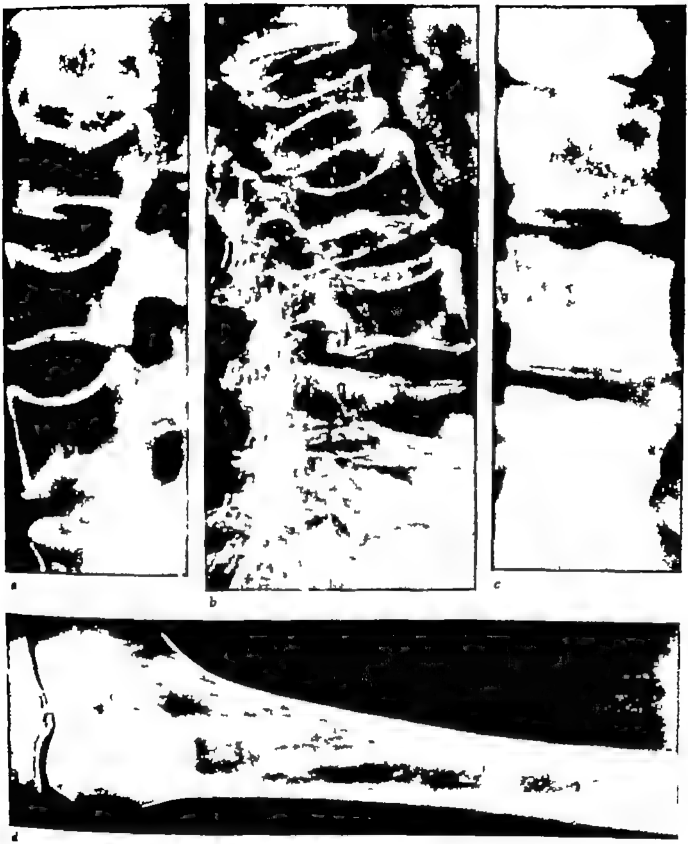


PLATE 1

a. Lumbar spine in POSTMENOPAUSAL OSTEOPOROSIS with marked resorption of the bone substance of the vertebral bodies. Impingement of the intervertebral disks, especially of the nuclei pulposi, into the weakened vertebral bodies has caused the formation of the hourglass or fish vertebrae.

b Lumbar spine in GAUCHER'S DISEASE, with comparable formation of hourglass vertebrae. Compression of all vertebral bodies, especially of L1 2 and 4. This roentgenologic picture cannot be differentiated from postmenopausal osteoporosis.

c. Initial stage of bone resorption of spine, irrespective of etiology Herniation of parts of the nucleus pulposus into the vertebral bodies; formation of Schmorl's nodules.

d. Femur in POSTMENOPAUSAL OSTEOPOROSIS. The normal cortex and spongiosa of the bones of the extremities are in sharp contrast to the marked resorption of bone in spine, ribs and pelvis.

PLATE 2

a Dorsal spine in POSTMENOPAUSAL OSTEOPOROSIS. Resorption of the bone substance of the vertebral bodies. Loss of the normal strength of the vertebrae as evidenced by the wedgelike compression of D10

b Dorsal spine in MULTIPLE MYELOMA resembling the roentgenogram in *a* Marked loss of the substance of the vertebral bodies, with ensuing decreased resistance as evidenced by the wedgelike compression of three dorsal vertebrae This roentgenologic picture cannot be differentiated from postmenopausal osteoporosis.

c AVITAMINOSIS C with calcification of the large subperiosteal hematomas. Clearcut osteoporosis of the distal part of the diaphysis (courtesy of Dr H J van Wersch, Heerlen, Holland).

d. LOOSER'S ZONE or MILKMAN'S FISSURE in apparently normal cortex, owing to osteomalacia.

e Marked thinning and lamellation of cortex of femur in AVITAMINOSIS D There is also widespread resorption of the trabecules of the cancellous bone.

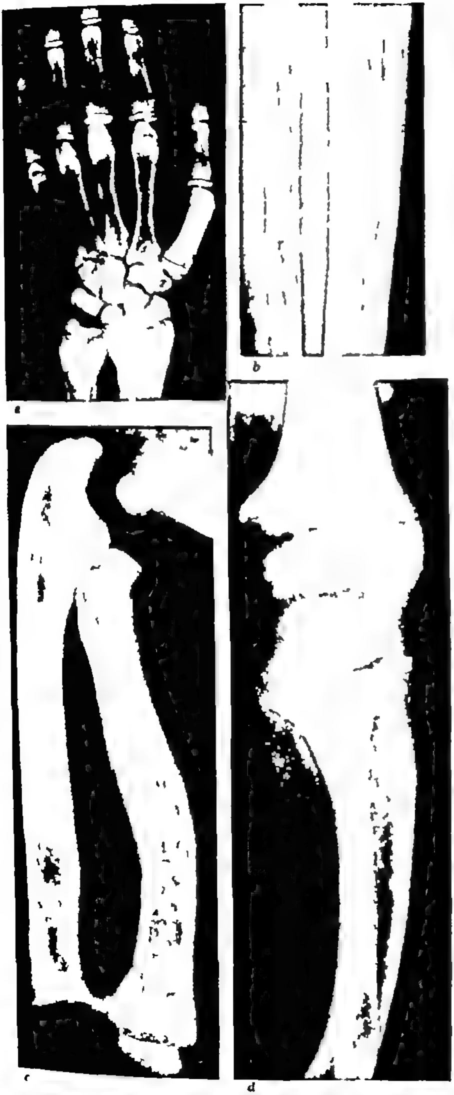


PLATE I

a. LATE RICKETS. Delayed closure of the epiphyseal disks. The disks of radius and ulna are swollen and the metaphyseal ends of the disks are frayed.

b. OSTEOMALACIA. Lamellation of the external cortex of the tibia. Thinning of the cortex of the fibula with a Looser's zone.

c and *d.* LIGNAC FANCONI DISEASE. Rickets manifested by the swelling and frayed character of the disks of the femur and the tibia. Note the frayed medial edge of the femoral epiphysis (courtesy of Dr R. Day, Department of Pediatrics, New York State University, Brooklyn, N. Y.).

PLATE 4

a. Pelvis in OSTEOMALACIA. Deformation of the left side of the pelvis with symphysiolysis. Folding of ischial bones. Coarse structure of bone caused by resorption of the secondary bone trabecules.

b. HYPERVITAMINOSIS D. Subcutaneous calcium deposits situated above the major trochanter and below the tuber ischii (*b* and *c* courtesy of Dr I. Dvore, Highland Park, Ill.).

c. Same patient as in *b* six months after cessation of vitamin D administration. The *calcium deposit below the ischial tuberosity has disappeared, but the supratrochanteric* calcification has remained unchanged.

a

b

c

PLATE 5

a. LATE RICKETS. Heart shaped deformity of the entrance of the lesser pelvis. Coarse structure of the bone substance results from resorption of the secondary bone trabecules. Folding of the ischial bones.

b OSTEOMALACIA (initial stage). The bone structure of the vertebral bodies is abnormal and fuzzy Collapse of vertebrae has not yet occurred.

c HYPERVITAMINOSIS D Marked resorption of bone in the lumbar spine, leading to vertical striation in the vertebral bodies (courtesy of Dr I. Dvore Highland Park, Ill.)

a

b

c

d

e

PLATE 6

a NEPHROCALCINOSIS. The grossly visible deposition of calcium is located in the medulla of the kidney around the renal pelvis and calyces. In the renal cortex, grossly no calcium deposits can be visualized.

b INFANTILE CORTICAL HYPEROSTOSIS with the characteristic hyperostosis of the clavicle (*b c d* and *e* courtesy of Dr J Caffey Babies Hospital, Columbia University New York, N Y).

c and *d*. INFANTILE CORTICAL HYPEROSTOSIS involving the shaft of the tibia in its entirety

e INFANTILE CORTICAL HYPEROSTOSIS showing characteristic involvement of the mandible.

a

c

PLATE 7

a. Hyperparathyroidism. Pelvis of patient treated with large doses of vitamin D and calcium. Marked reossification of the giant cell tumors of the right pubic bone, right wing of sacral bone and left iliac bone. Moderate reossification of a giant cell tumor of the right femur. Considerable deterioration of renal function developed during this treatment.

b. Hypervitaminosis A. Cortical hyperostosis of the 3rd and 4th metatarsal bones.

c. Hypervitaminosis A. Cortical hyperostosis of the lateral and medial aspects of the ulna. The new formation of bone involves only part of the diaphyseal shaft.

a

b

c

PLATE 8 HYPERPARATHYROIDISM

a. Skull after administration of large doses of vitamin D and calcium. Marked reossification of giant cell tumors present in left zygoma and left mandible. Considerable deterioration of renal function developed during this treatment.

b Giant cell tumors of lower end of humerus and upper end of ulna.

c Cystlike lesion within the cortex of the femur Lamellation of the femur cortex by osteitis fibrosa. Resorption of bone in the spongiosa. The cystlike lesion rapidly reossified after operation and therefore probably represented a giant cell tumor

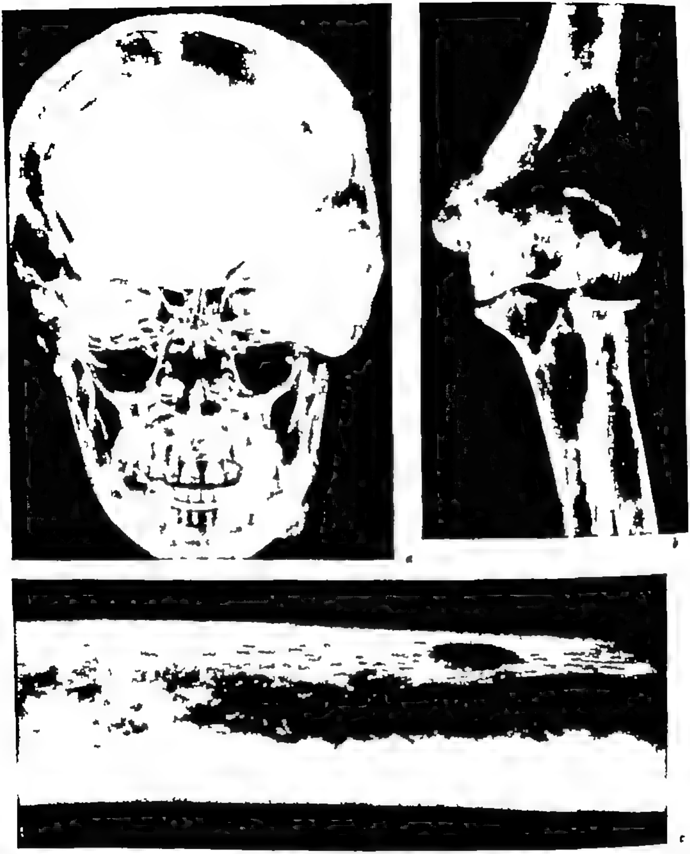
a

b

PLATE 9. Hyperparathyroidism

a. Motheaten skull before operation. Osteitis fibrosa causing numerous small areas of resorption of bone, leading to the characteristic roentgenologic appearance of the calvarium.

b. Return to normal one year after removal of the parathyroid adenoma.



a b c

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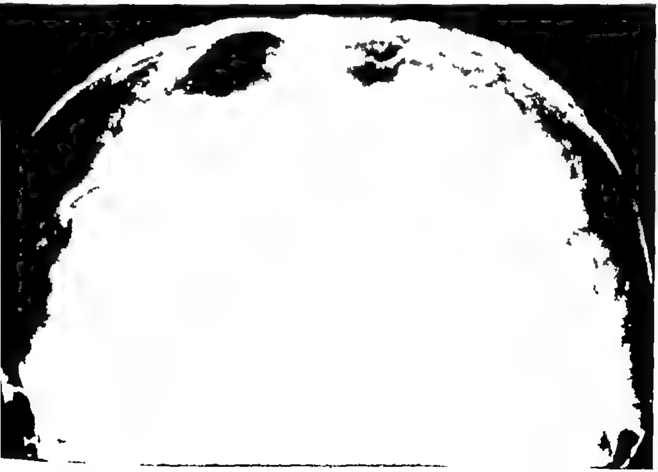
a



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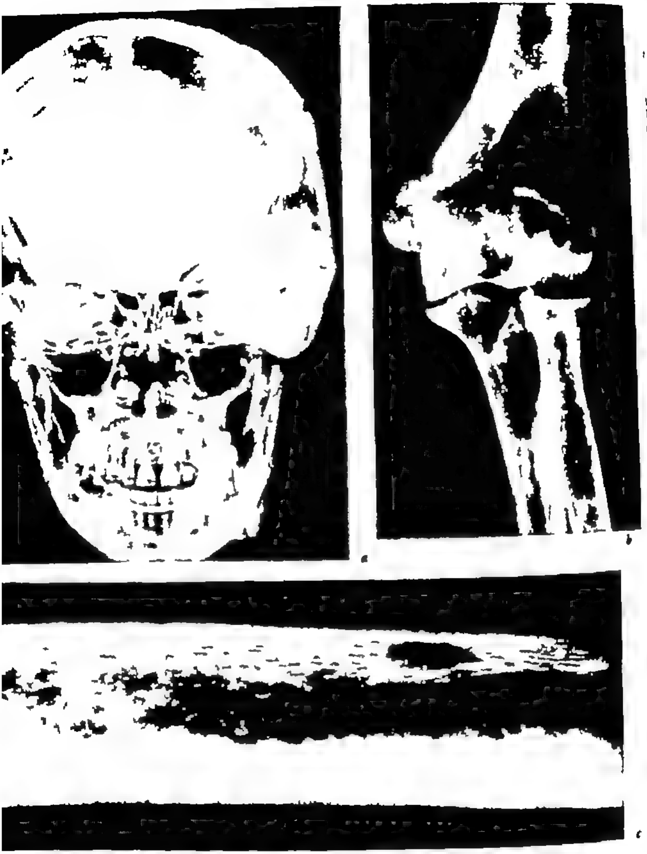

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PLATE 11
Hyperparathyroidism

a Crescent-shaped osteolytic lesion of the mandible which at biopsy proved to be an osteoclastoma The tumor was removed by block resection. Four years later the patient was found to be suffering from hyperparathyroidism

b Intact lamina dura in a patient with proved hyperparathyroidism Nevertheless bone resorption must have been intense as evidenced by the wide meshed structure of the cancellous bone of the jaw and the reduced diameter of the bone trabecules.

c and *d* Disappearance of lamina dura in hyperparathyroidism (courtesy of Dr Lester Cahn, New York, N Y).

b

c

d

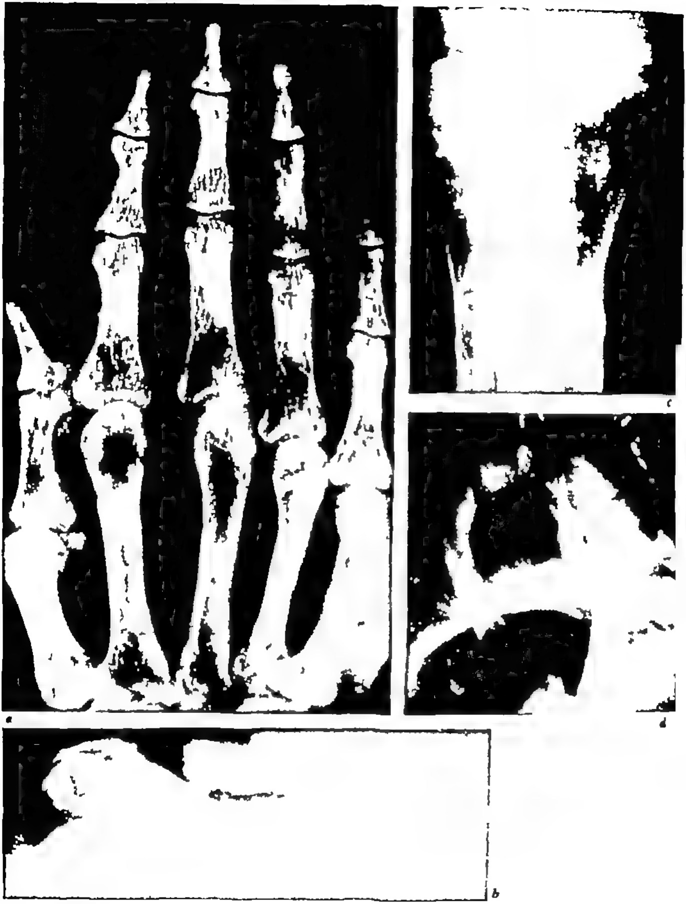

PLATE 10. HYPERPARATHYROIDISM

a. Skeleton of hand with marked generalized resorption of bone throughout. There is also subperiosteal resorption of bone, most marked in the second phalanx of the 2nd and 3rd fingers, leading to a concave configuration of the radial aspect of these phalanges. Giant cell tumor of fifth metacarpal.

b. Subperiosteal resorption of bone leading to a complete disappearance of the lateral end of the clavicle.

c. Subperiosteal resorption of bone of the lateral aspect of the upper part of the tibia.

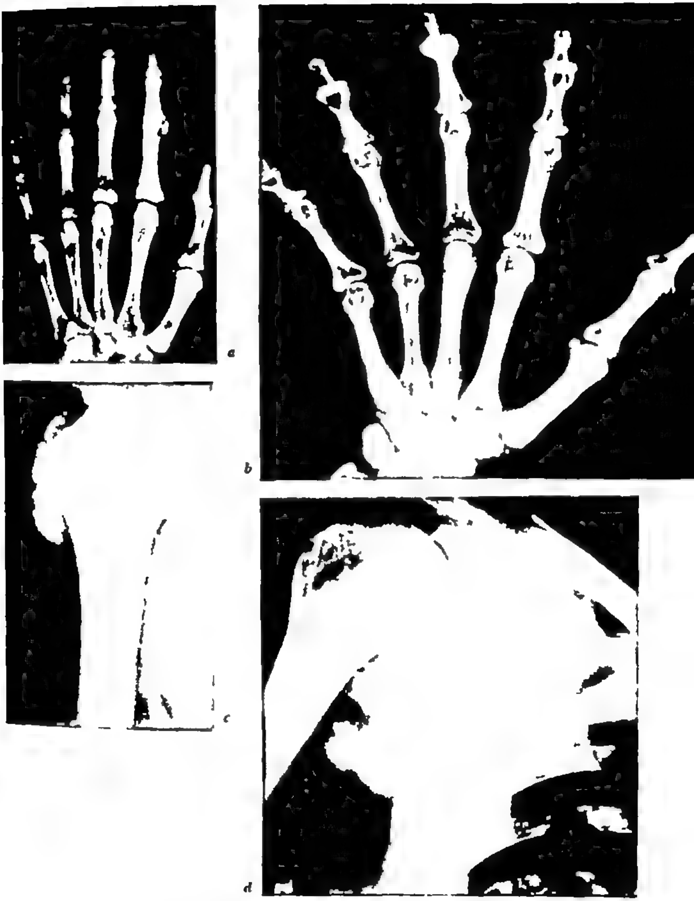

PLATE 15

a. RENAL OSTEITIS FIBROSA. Diffuse resorption of the bone of the hand skeleton. Synovial calcinosis in the proximal interphalangeal articulation of index finger

b. BOECK'S SARCOIDOSIS. Cystlike osteolytic lesions in the distal phalanx of the thumb and in the 2nd and 3rd phalanges of the other fingers. There are less distinct lesions in the heads of the 1st phalanges and in the 5th metacarpal bone (courtesy of Dr M Gellis, Health Department of the City of New York)

c and *d.* ALKALI-MILK SYNDROME or BURNETT'S SYNDROME. Large calcium deposits are present in the subdeltoid and subscapular bursae.

a

b

c

PLATE IX Renal Osteitis Fibrosa

a. Anterior Posterior View Impingement of the shaft of the left femur into the softened epiphysis. The structure of the metaphysis and the epiphysis is abnormal and the cortex of the femur tibia and fibula is markedly thinned.

b Lateral View Impingement of the shaft of the right femur into the softened epiphysis. The structure of the metaphysis and the epiphysis of both femur and tibia is abnormal. Thinning of the cortex of the femur tibia and fibula.

c Elbow with subcutaneous calcium phosphate deposits near the upper part of the ulna In this case there is no marked resorption of bone

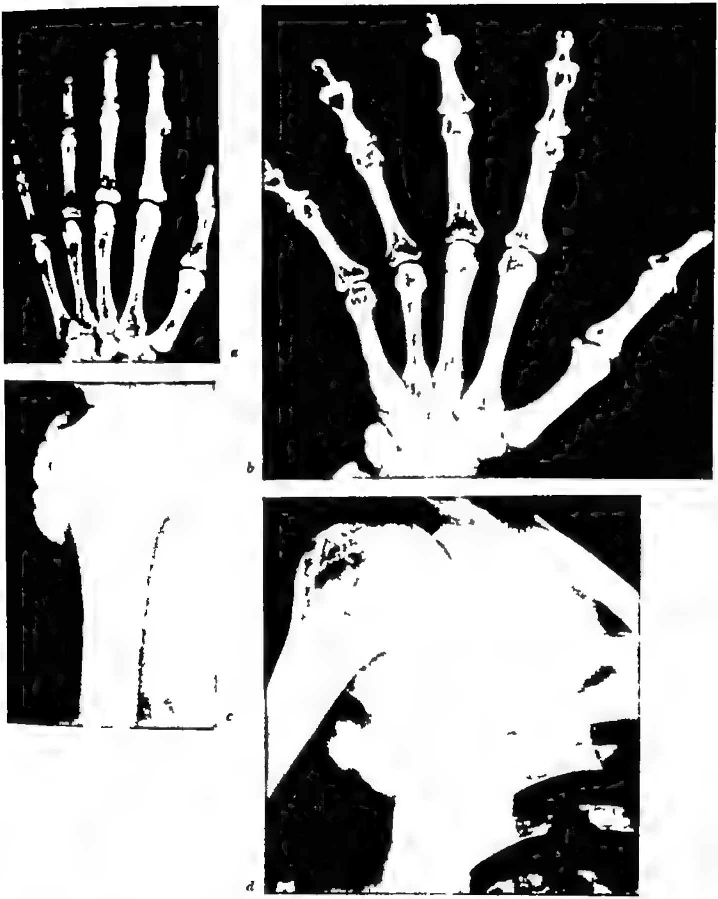

PLATE 13

a. RENAL OSTEITIS FIBROSA. Diffuse resorption of the bone of the hand skeleton. Synovial calcinosis in the proximal interphalangeal articulation of index finger

b BOECK'S SARCOIDOSIS. Cystlike osteolytic lesions in the distal phalanx of the thumb and in the 2nd and 3rd phalanges of the other fingers. There are less distinct lesions in the heads of the 1st phalanges and in the 5th metacarpal bone (courtesy of Dr M Gellis, Health Department of the City of New York)

c and *d* ALKALI MILK SYNDROME or BURNETT'S SYNDROME. Large calcium deposits are present in the subdeltoid and subscapular bursae.

a

b

c

PLATE 14

a PSEUDOHYPOPARATHYROIDISM. Characteristic shortening of the 4th and 5th metacarpal bones. Likewise shortening and broadening of the 1st metacarpal bone and the 2nd phalanx of the index finger. There is also subcutaneous bone formation at the ulnar aspect of the head of the 2nd metacarpal (courtesy of Dr Theodore B Schwartz, Presbyterian Hospital, Chicago, Ill.).

b IDIOPATHIC HYPOPARATHYROIDISM with generalized bone resorption. The coarse bone structure in the head of the humerus is owing to the resorption of secondary bone trabecules.

c HYPOPARATHYROIDISM. Calcification of the basal ganglia.

PLATE 15

a PAGET'S DISEASE. Typical cottonwool structure of calvarium. Marked thickening of the internal table with irregular calcification of the diploe. The diameter of the skullcap is considerably increased. Notwithstanding the thickening of the skull the resistance of the bone is diminished and the impingement of the cervical spine upon the base of the skull has caused platybasia.

b and *c* IDIOPATHIC HYPOPARATHYROIDISM with generalized resorption of bone. Increase of the diameter of the intervertebral disks with ensuing compression of several vertebrae *(courtesy* of Dr Joseph E Pincus, Brooklyn Jewish Hospital, Brooklyn N Y).

d Abnormalities of the enamel of the teeth in IDIOPATHIC HYPOPARATHYROIDISM.

PLATE III PAGET'S DISEASE

Left half of pelvis and left femur are markedly sclerotic. Right half of pelvis and right femur are completely normal. In the upper lateral part of the left iliac bone, coarse and abnormally arranged trabecules are present. The diameter of both the sclerotic pubic and ischial bones is increased, compared with the normal side

The left femur head is completely sclerotic. The diameter of the diaphysis of the left femur is greater than that of the normal femur The cortex is much increased in diameter but part of the marrow cavity still remains. Notwithstanding the sclerotic character of the left femur the solidity and the resistance of the bone are impaired as evidenced by the abnormal position of the left femur neck with ensuing apposition of the left major trochanter against the iliac bone.

PLATE 16 PAGET'S DISEASE

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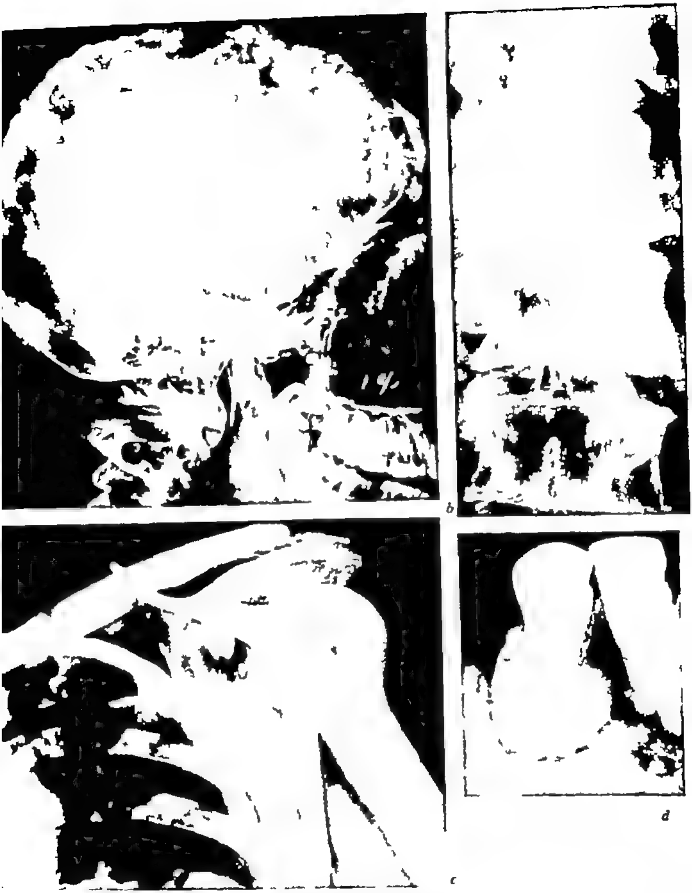


PLATE 17 Paget's Disease

a Typical cottonwool pattern of the skull with irregular sclerosis of the calvarium, especially in the posterior part of the skull. In addition there is osteoporosis circumscripta cranii, only a central triangular pyramid of normal bone has remained.

b Sclerotic Paget's disease involving the 1st lumbar vertebra in its entirety and the greater part of the 2nd lumbar vertebra.

c Sclerotic Paget's disease of the clavicle and the humerus. The normal bone structure of the clavicle and the head of the humerus has completely disappeared and is replaced by a sclerotic mass. In the diaphysis of the humerus, the original cortex is still faintly visible but is surrounded by a thick layer of newly formed periosteal bone. The marrow cavity has remained intact.

d Periapical cementosis in Paget's disease (courtesy of Dr Lester Cahn New York, N Y).

PLATE 18 PAGET'S DISEASE

a Compression of the 9th dorsal vertebra from Paget's disease, as evidenced by thickening and sclerosis of both superior and inferior terminal plates. Elongation of the anterior posterior diameter of the compressed vertebra another frequent manifestation of Paget's disease, is present (courtesy of Dr M Dannenberg, Brooklyn N Y).

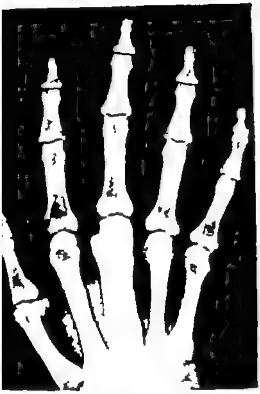
b Increased diameter of the humerus with abnormal arrangement and architecture of thickened bone trabecules, causing profound changes of the structure of both cortex and cancellous bone

c Thickening of the cortex and abnormal architecture of the cancellous bone of the tibia Notwithstanding the thickened cortex the solidity of the bone has decreased, as evidenced by the bowing of the tibia in contrast to the completely normal fibula.

d Compression of the sclerotic 12th dorsal vertebra with elongation of the transverse diameter as typical of Paget's disease.

a

b



c

e

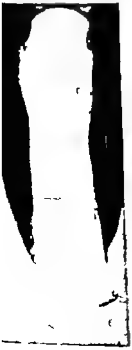


PLATE 19 PAGET'S DISEASE

a and *b* Normal right foot, compared with the left foot affected by Paget's disease. In the latter sclerosis and thickening of the cortex of the calcaneus are present, with coarsening of the bone trabecules of the cancellous bone There are comparable changes in the calcaneus spur of the left foot.

c Sclerotic and thickened metacarpal of a patient with leontiasis ossea due to Paget's disease (Plate 28) Paget lesions of the skeleton of the hand are comparatively rare.

d. Same metacarpal as in *c* in natural size.

e Involvement of the head of the humerus, glenoidal fossa, clavicle coracoid process and ribs in Paget's disease In all these bones, coarse and abnormally arranged bone trabecules are found. In the humerus, clavicle, scapula and first rib marked thickening and sclerosis of the cortex are present. Such involvement of one or more ribs is a rare occurrence in Paget's disease.

In the humerus head there is a pseudocystic cavity probably filled with fat.

d

PLATE 20 · PAGET SARCOMA

The left half of the pelvis and the intra-acetabular part of the femur head are sclerotic. The diameter of the left pubic and ischial bones is increased, compared with the normal side. The cortex of the left pubic and ischial bones is thickened.

In the upper third of the right femur there is a large osteolytic lesion, which has led to extreme thinning of part of the lateral cortex of the femur. Biopsy revealed the presence of an osteogenic sarcoma.

a

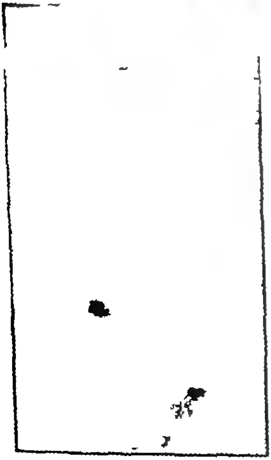
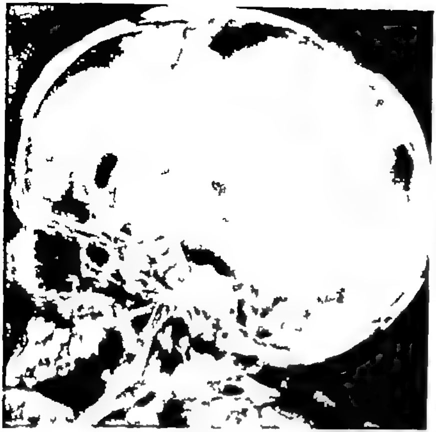


PLATE 21 Paget Sarcoma

a Osteosclerotic form of Paget's disease involving the pelvis in its entirety and both femurs. There is a deformity of the lesser pelvis owing to the intrusion of the heads of the femora into the softened pelvis. The diameter of the cortex of the femur is increased and the structure of the cancellous bone is abnormal. In addition there is a large osteolytic lesion of the left ischial bone as a result of osteogenic sarcoma.

b The sarcomatous lesion of the left ischial bone of *a* in natural size.



a

b

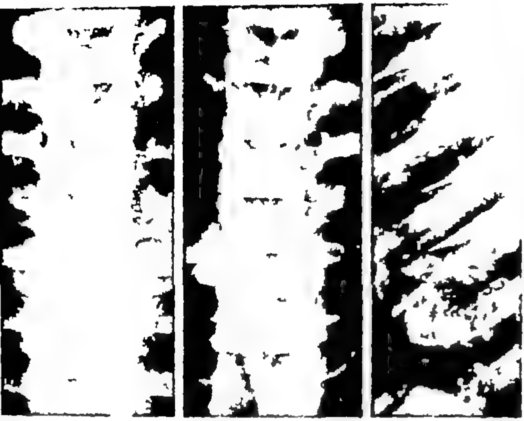
c

PLATE 22

a HAND-SCHÜLLER-CHRISTIAN DISEASE *Multiple sharply circumscribed areas of bone resorption, owing to lipoid granuloma, are present in the skull.* The truly destructive character of the lesion *is clearly visualized on the tangential* aspect of the calvarium. The osteolytic areas are *not surrounded* by a sclerotic rim. There are also several lipoid granulomas *in* the mandible.

b EPIDERMOID CYST OR CHOLESTEATOMA OF THE SKULL. There is a sharply circumscribed area of bone resorption which can be distinguished from lipoid granulomatosis by the surrounding thick osteosclerotic rim.

c EOSINOPHILIC GRANULOMA of the iliac bone presenting as a cluster of multiple, well-circumscribed osteolytic lesions (courtesy of Dr M Dannenberg, Brooklyn N Y)



a b c

d

PLATE [illegible]

a EOSINOPHILIC GRANULOMA of 8th dorsal vertebra. The right half of the vertebral body is collapsed, but the intervertebral disks and the pedicles are intact (*a* *b* and *c* courtesy of Dr Joseph B Pincus, Brooklyn Jewish Hospital Brooklyn N Y).

b Later stage. Now the vertebral body is completely collapsed and only a thin bone plate is left. Formation of a biscuit or silver dollar vertebra.

c Lateral view of the same vertebra (the third from below). The vertebral body presents as a narrow band of bone. This is an example of a typical "vertebra plana" as described by Calvé.

d POLYOSTOTIC FIBROUS DYSPLASIA of two adjoining ribs. Pseudocystic transformation of the ribs, with tremendous increase of diameter

PLATE 24

Hand of a patient with polyostotic fibrous dysplasia. There is an increase of the diameter and a change in the bone structure of the 1st, 2nd and 4th metacarpals. Nearly all the phalanges are broadened and exhibit an abnormal structure. Only the 2nd phalanx of the 3rd finger and the terminal phalanx of the 2nd 3rd and 5th fingers are apparently normal.

The increase of the diameter is caused by proliferation of a firm fibrous tissue, arranged in whorls, which destroys and replaces the cancellous bone and compresses the cortex to a paper thin line. The same process is present in the terminal end of the radius (courtesy of Dr Ray F Farquharson Department of Medicine University of Toronto).

a

b

PLATE 25 Polyostotic Fibrous Dysplasia

a Pelvis and femora of a child with a grotesque deformation of the left half of the pelvis caused by compression of the softened pelvic bone by the left femur There is a marked increase of the diameter of the left pubic, ischial and iliac bones and of the left femur owing to the proliferation of firm fibrous tissue. The latter has completely changed the structure of the bone and has led to compression of the cortex.

b Femur with marked bowing of the diaphysis and deformation of the neck and the shaft of the femur The structure of the cancellous bone is abnormal because of the proliferating fibrous tissue which in several places has become sclerotic. The cortex is compressed mainly in the lateral aspect of the upper third of the diaphysis, neck and head of the femur

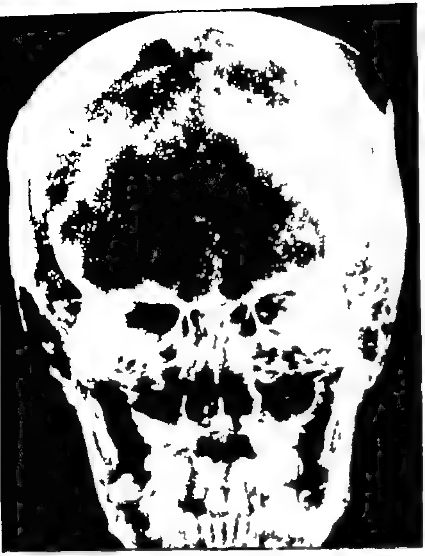
a

b

PLATE 26 Polyostotic Fibrous Dysplasia

a The softened bones of this pelvis of an adult patient are compressed by the femora leading to deformation of the lesser pelvis. Pseudocystic changes are spread throughout the pelvis and the femora. There is bowing of the femur shafts and necks. The latter has led to opposition of both major trochanters against the iliac bone. The structural changes of the femora are the same as described in the legend of Plate 25 (courtesy of Dr Ray F Farquharson Department of Medicine University of Toronto).

b Humerus of an adult with polyostotic fibrous dysplasia presenting as pseudocystic lesions within the cancellous bone mainly in the upper part of the diaphysis.



a

b

c

PLATE 27 POLYOSTOTIC FIBROUS DYSPLASIA

a. SUBPERIOSTEAL PSEUDOCYSTIC LESION in the skull. The pseudocystic area derives from proliferation of hard fibrous tissue.

b Pigmentation with jagged contours on the back of the same patient as in *a* 30 years previous to the roentgenogram of the skull.

c Young man with LEONTIASIS OSSEA, possibly the result of polyostotic fibrous dysplasia. In the left orbit, an abnormal swelling of the lesser part of the greater wing of the sphenoid bone can be seen. Other roentgenograms, not shown here, reveal a compression of the left optic foramen. Sclerosis of the zygomatic bone is also present.

a

b

PLATE 26 POLYOSTOTIC FIBROUS DYSPLASIA

a The softened bones of this pelvis of an adult patient are compressed by the femora leading to deformation of the lesser pelvis. Pseudocystic changes are spread throughout the pelvis and the femora. There is bowing of the femur shafts and necks. The latter has led to opposition of both major trochanters against the iliac bone. The structural changes of the femora are the same as described in the legend of Plate 25 (courtesy of Dr Ray F Farquharson, Department of Medicine, University of Toronto).

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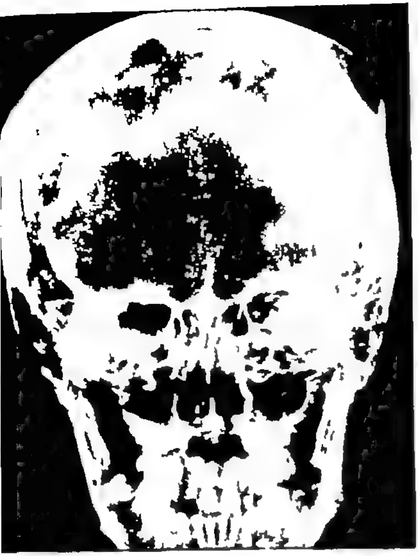


a

b

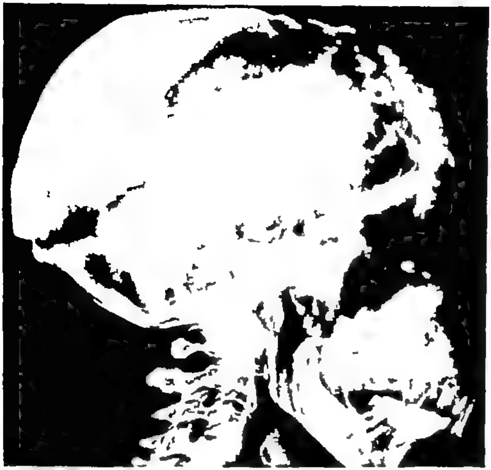
c

PLATE 27 Polyostotic Fibrous Dysplasia

a Subperiosteal pseudocystic lesion in the skull. The pseudocystic area derives from proliferation of hard fibrous tissue.

b Pigmentation with jagged contours on the back of the same patient as in *a* 30 years previous to the roentgenogram of the skull.

c Young man with leontiasis ossea, possibly the result of polyostotic fibrous dysplasia. In the left orbit, an abnormal swelling of the lesser part of the greater wing of the sphenoid bone can be seen. Other roentgenograms, not shown here reveal a compression of the left optic foramen. Sclerosis of the zygomatic bone is also present.



a

b

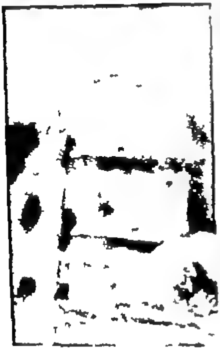
PLATE 28

a. Skull of patient with LEONTIASIS OSSEA combined with OSTEOPOROSIS CIRCUMSCRIPTA CRANII. The latter in addition to the cottonwool character of the skull favors a diagnosis of Paget's disease. Marked sclerosis of the base of the skull. Note the abnormal structure of the maxillary bone, owing to osteitis fibrosa.

b Skull of child with LEONTIASIS OSSEA. In view of the patient's age (9 years) and the characteristic hyperostosis at the occipital squama, the leontiasis ossea is probably the result of polyostotic dysplasia. Nevertheless, the structure of the calvarium is highly reminiscent of a cottonwool skull, often considered pathognomonic of Paget's disease. There is marked sclerosis of the base of the skull. The structure of the maxillary bone is abnormal, owing to proliferating fibrous tissue.

a

b



d

e

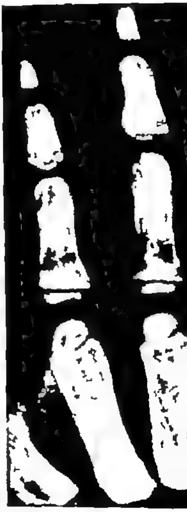


PLATE 29

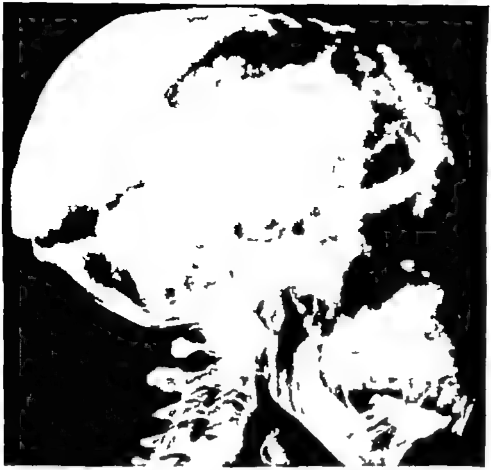
a. Hairbrush skull in THALASSEMIA. Increased diameter of the diploe of the calvarium with thinning of both the external and the internal tables and vertical striation. All these anomalies derive from proliferation of the erythroblastic bone marrow

b. Hand of a child with THALASSEMIA. Increased diameter of the bones with thinning of the cortex and abnormal structure of the cancellous bone, caused by the same process.

c. Second and third fingers of *b* in natural size.

d. SICKLE CELL ANEMIA in a middle aged patient. Compression of the softened lumbar vertebrae by the intervertebral disks with formation of hourglass vertebrae. The softening of the bone must have taken place during the acute stage of the disease in childhood the sclerosis at a later age when the disease was burnt out.

e. Deformity and collapse of the head of the femur with osteosclerosis in the same patient as in *d* possibly owing to infarction of the bone.



a

b

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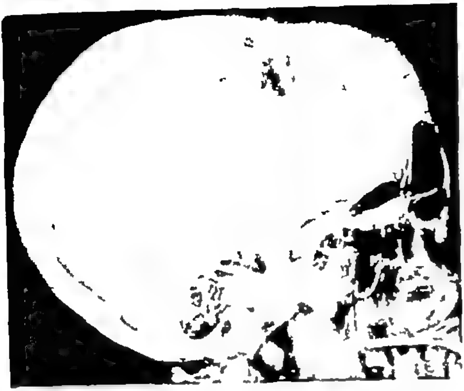
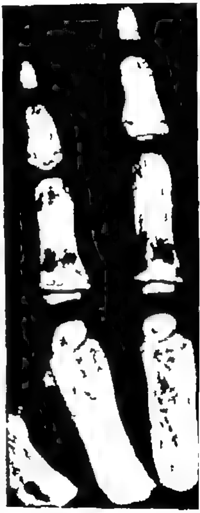


a

b

d

e



c

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b Hand of a child with THALASSEMIA. Increased diameter of the bones with thinning of the cortex and abnormal structure of the cancellous bone, caused by the same process.

c Second and third fingers of *b* in natural size.

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e Deformity and collapse of the head of the femur with osteoscle rosis in the same patient as in *d* possibly owing to infarction of the bone.

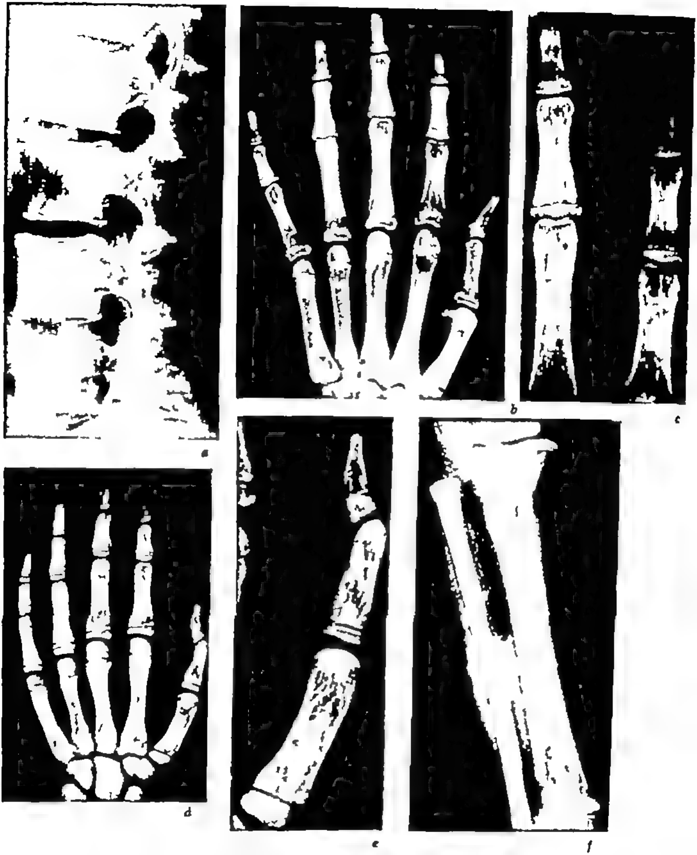


PLATE 30

a. Spine of patient with THALASSEMIA. Multiple tiny areas of bone resorption caused by the proliferation of the erythroblastic marrow

b Hand of same patient as in a with multiple small pseudocystic areas, mainly in the phalanges, caused by the same process.

c Second and third finger of *b* in natural size.

d. Hand of a child with SUBACUTE LYMPHATIC LEUKEMIA. Multiple small irregular areas of bone resorption are seen, mainly in the first metacarpal bone and thumb less in the other bones of the hand. These lesions had caused the clinical picture of "acute rheumatoid arthritis" of the fingers.

e Thumb of *d* in natural size.

f ACUTE LEUKEMIA in childhood. Symmetric resorption of bone in both upper and lower metaphyses with elevation of the periosteum of the lateral aspect of the tibia.

a

b

c

PLATE 31 Hodgkin's Disease

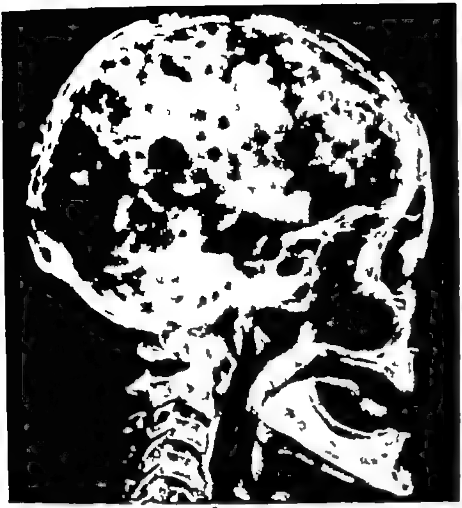
a Skull with large osteolytic lesion diagnosis of Hodgkin's disease proved by biopsy

b Hodgkin's disease leading to moderate sclerosis of the 10th and 11th dorsal vertebrae. This patient developed a paraplegia, and microscopic examination of the tissue obtained during the laminectomy proved the diagnosis.

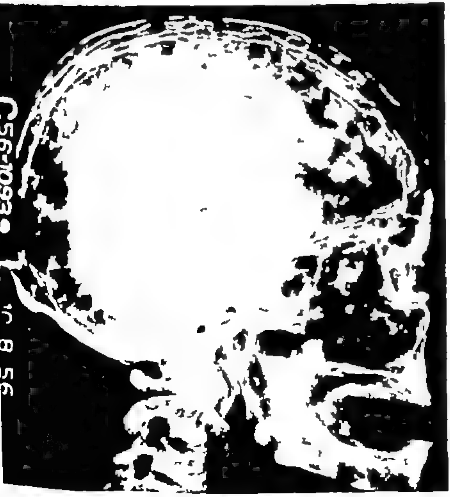
c Hodgkin's disease leading to an extensive osteolytic lesion in the 11th and 12th dorsal vertebrae. The left pedicle of the 11th vertebra is completely destroyed the right pedicle is partly eroded. The diagnosis was proved during a laminectomy necessitated by a paraplegia.

PLATE 32 Hodgkin's Disease

The disease has here given rise to a sclerosis of the wings of the sacrum and of the medial parts of both iliac bones. Moderate sclerosis is present in the lateral wing of the left iliac bone. This patient had a large abdominal tumor and the diagnosis was proved during exploratory laparotomy



a



b

PLATE 33 LYMPHOSARCOMA OF THE SKULL

a The calvarium is riddled by numerous punched out, sharply defined round osteolytic areas which are not surrounded by a sclerotic rim. There are a few osteolytic lesions in the mandible. Although the possibility of a multiple myeloma could not be excluded, a biopsy of the skull showed the presence of lymphosarcoma.

b Same skull 10 months later The osteolytic process has rapidly progressed and the myeloma-like picture has disappeared. Many new osteolytic lesions have developed in the mandible.

PLATE 34 ALEUKEMIC MEGAKARYOCYTIC LEUKEMIA

(leading to osteosclerotic and osteolytic lesions in the same patient)

a Osteosclerosis of the dorsal vertebrae.

b Marked osteosclerosis of the lumbar vertebrae.

c Humerus of the same patient, with numerous osteolytic areas, especially in the upper and lower third of the diaphysis.

d Part of the femur of the same patient, with numerous osteolytic areas.

b

PLATE 35

a. Multiple myeloma. Pelvis, with numerous small osteolytic lesions spread through all the pelvic bones. Both femora are similarly affected. Generalized marked resorption of bone substance with thinning of the cortex throughout. There is also a fracture of the right ischial bone.

b Plasmocytoma of the right iliac bone. Septate lesion which could be confused with a giant cell tumor. Although the rest of the pelvis seemed roentgenologically to be normal, bone marrow puncture revealed the presence of generalized myelomatosis.

a

b

PLATE 38

a. MULTIPLE MYELOMA. Widespread and severe bone resorption affecting all the vertebral bodies, the pedicles and the spinous processes. The cortex of the vertebrae is paper thin. The 1st lumbar vertebra is completely collapsed, but the intervertebral disks are intact. Another example of myeloma of the spine is shown in Plate 1

b. MULTIPLE MYELOMA giving rise to a collapse of the 11th and 12th dorsal vertebrae. In this case the intervertebral disk has completely disappeared, which is a rare occurrence in myeloma.

c. Femur with MULTIPLE PLASMOCYTOMAS in a patient with MYELOMA. The large punched out lesions, without an osteosclerotic rim, are characteristic of the disease.

a

d

b

c

PLATE 37

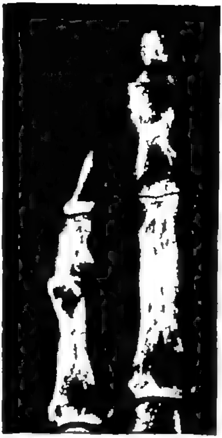
a. Skull in MULTIPLE MYELOMA with multiple small punched out lesions, without a sclerotic rim. One osteolytic lesion is present near the angle of the mandible.

b. Skull in MULTIPLE MYELOMA with widespread large and small osteolytic lesions. Several osteolytic lesions are present in the mandible.

c. RETICULUM CELL SARCOMA of the humerus. These circumscribed osteolytic lesions could be distinguished from myelomatosis only by microscopic examination.

d. Fracture of the sternum in MULTIPLE MYELOMA.

a



b

c

d

e

PLATE 38 Gout

a. Large destructive tophi in the 4th and 5th fingers. The distal interphalangeal joint of the 4th finger and the proximal interphalangeal joint of the 5th finger are destroyed.

b Fourth and 5th fingers of *a* in natural size.

c Small tophi in the distal end of the 1st phalanx and the proximal end of the 2nd phalanx of the thumb.

d. Many extensive osteolytic lesions owing to the presence of large tophi The tophi are localized in the tarsal bones and in the proximal ends of the 3rd, 4th and 5th metatarsals. Destruction of joints.

e Tarsal bones and proximal parts of metatarsal bones of *d* in natural size

PLATE 39 GAUCHER'S DISEASE

Multiple areas of bone resorption, spread through the cancellous part of the femora, caused by the proliferating Gaucher cells. This has also led to thinning of the cortex of the distal ends of the femora, and to moderate swelling of the supracondylar parts of the femora. In this case there are no typical "Erlenmeyer flask" like changes.

a

b

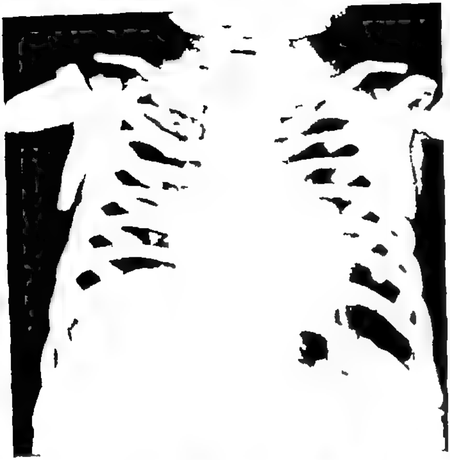
c

PLATE 40 GAUCHER'S DISEASE

a Deformity and sclerosis of the head and neck of the femur probably owing to infarction after the closure of blood vessels by Gaucher cells. Arthritis-like changes of the articular surfaces of the hip joint.

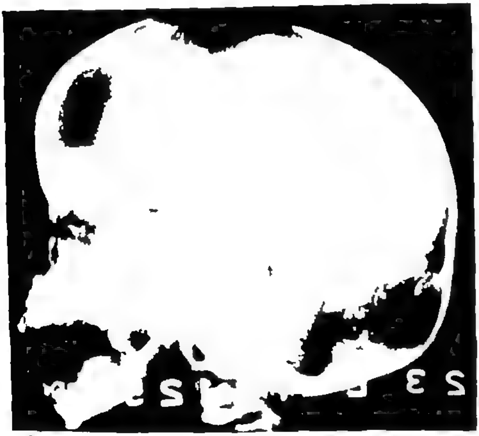
b Atrophy of the cortex of the head and neck of the humerus, caused by proliferation of Gaucher cells.

c. Hand of the same patient as in *b* with marked and extensive resorption of bone from the entire skeleton of the hand and the lower parts of the radius and ulna. Compare with the marked decalcification of the spine and vertebral compression of the same patient (Plate 1*b*).



a

c



b

PLATE 41 OSTEOPETROSIS

a. Infantile form. The entire skeleton of the thorax consists of marble bones. Note characteristic clubbing of the proximal part of the humerus (*a* *b* and *c* courtesy of Dr Joseph B. Pincus, Brooklyn Jewish Hospital, Brooklyn, N Y).

b Same patient. Marked marble bone formation at the base of the skull. Note thickening of the posterior clinoid processes of the sella turcica.

c Same patient. The skeleton of the lower extremities also consists of bones. Note the characteristic clubbing of the ends of the extremities.

a

b

c

PLATE 42. OSTEOPETROSIS

a Skull of a child with osteopetrosis.

b Hand of an adult with osteopetrosis. Note the sclerotic bone rings in the 1st metacarpal and phalangeal bones. Thickening of the cortex of bones, but the bone marrow cavity is not completely obliterated (courtesy of Dr L Bluth, Brooklyn, N Y).

c Foot of another adult with osteopetrosis. Remnants of the marrow cavity are still present in the distal part of the 1st metatarsal and the proximal part of the 2nd, 3rd, 4th and 5th metatarsals.

PLATE 43 OSTEOPETROSIS

Vertebral column ribs and pelvis of an adult with osteopetrosis. There is marked thickening of the cortex of the vertebrae with conservation of the marrow space in the central part of the vertebral bodies, leading to the formation of "sandwich vertebrae."

In the iliac bones of the osteopetrotic pelvis, a characteristic circular pattern is clearly visible.

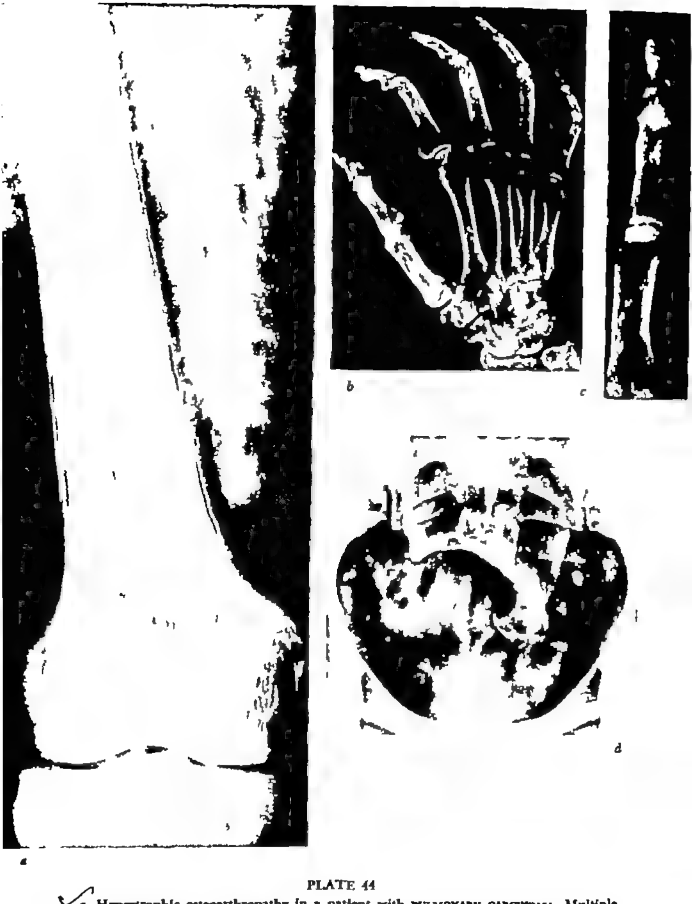


PLATE 44

a. Hypertrophic osteoarthropathy in a patient with PULMONARY CARCINOMA. *Multiple layers of ossifying periostitis surrounding the shaft of the femur*

b SCLERODERMA with necrosis of the ends of the terminal phalanx of the 1st, 2nd, 3rd and 4th fingers. Incomplete destruction of the nonsclerotic part of the phalanges.

c Thumb of *b* in natural size.

d. NEUROFIBROMA of the sacrum, leading to destruction of the greater part of the right lower sacrum.

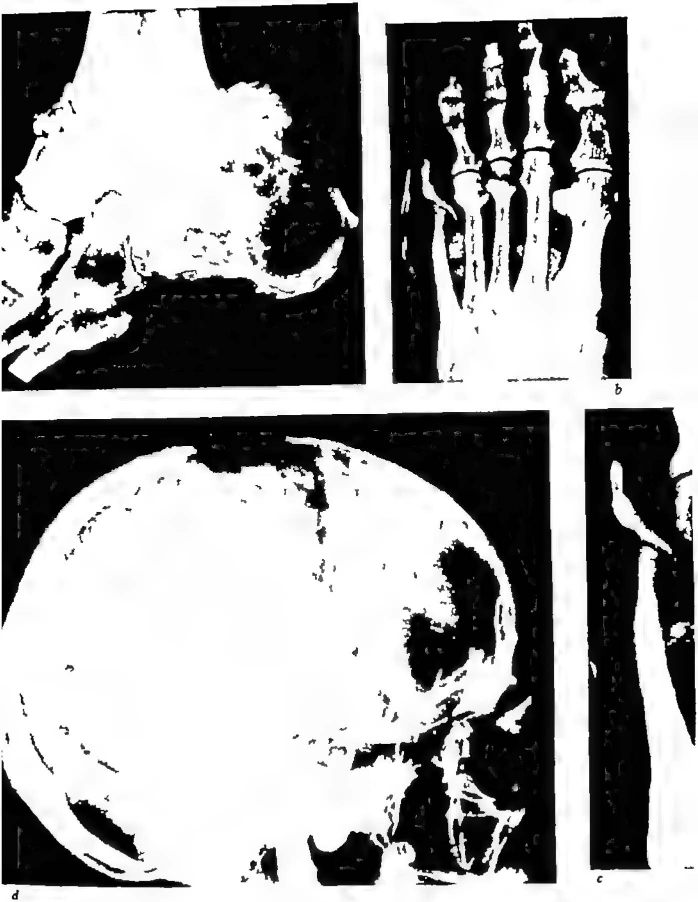


PLATE 45

a. TABETIC ARTHROPATHY of the ankle joint (Charcot joint) Osteosclerosis with extensive periarticular proliferation of bone.

b Tabetic changes of the 5th toe. Candlestick deformity of the terminal end of the 5th metatarsal bone with necrosis of the phalanges of the 5th toe.

c Fifth metacarpal and toe of *b* in natural size.

d. METASTASIS OF A THYROID CARCINOMA to the skull Pr[illegible] of the superior part of the calvarium without any sclerosis.

a

b

c

d

PLATE 46

a. METASTATIC MAMMARY CARCINOMA, osteoblastic in nature. Marked osteosclerotic changes of pelvis and femur Amidst the sclerotic bone, osteolytic lesions can be seen in the iliac bone near the superior and inferior iliac spine in both ischial bones and in the major trochanter of the femur Pathologic fracture of the femur

b Osteoblastic METASTATIC LESIONS of a MAMMARY CARCINOMA to the spine. In addition, osteolytic lesions in the 2nd, 3rd, 4th and 5th lumbar vertebrae.

c. Multiple OSTEOLYTIC METASTATIC LESIONS of a MAMMARY CARCINOMA to the skull. The lesions are less sharply punched out than in myeloma.

d. METASTASIS OF A THYROID CARCINOMA to the head of the humerus. Purely osteolytic cystlike lesion.

PLATE 47

Osteoblastic METASTASES of a PROSTATIC CARCINOMA in the 3rd and 5th lumbar vertebrae, leading to the formation of ivory vertebrae. There are large osteoblastic metastatic masses in the sacrum and the iliac bones.

a b c d

PLATE 48

a. CHRONIC SYPHILITIC OSTEOMYELITIS. The gummous osteomyelitis of the upper three-fourths of the tibia has led to an irregular sclerosis of the shaft in which many osteolytic areas are present. In the middle of the fibula there is another area of syphilitic osteomyelitis with marked periostitis.

b and *c.* Osteolytic lesions due to COCCIDIOIDOMYCOSIS of the 8th and 11th ribs. In this case no sclerosis of bone has developed.

d. SALMONELLA OSTEOMYELITIS of the spine. Complete disappearance of the epiphyseal disk between the 11th and 12th dorsal vertebra. The pedicles are intact. Moderate, irregular sclerosis is present in the lower end of the 11th dorsal vertebra.